Unlicensed and off-label drug use in paediatrics in a mother-child tertiary care hospital

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OBJECTIVE: To assess unlicensed and off-label drug use in a tertiary care paediatric hospital in Canada on a single day.
METHODS: A cross-sectional study in a tertiary care paediatric hospital was conducted on one randomly selected day. Active prescriptions for children <18 years of age were analyzed. Unlicensed drug use was defined as the use of nonmarketed drugs in Canada or marketed drugs with pharmacy compounding. Off-label drug use was defined as the use of marketed drugs in Canada for an unapproved age group, indication, dosing, frequency and/or route of administration. Off-label drug uses associated with strong scientific support were analyzed using the *Pediatric Dosage Handbook, 14th edition* and Micromedex® Solutions. Number and proportion of unlicensed and off-label drug uses, and off-label drug uses associated with strong scientific support were measured.
RESULTS: A total of 2145 drug prescriptions were extracted on March 5, 2014, for inclusion in the present study. The unlicensed drug use rate was 8.3% (57 unlicensed drug products; 75 nonmarketed drug prescriptions and 103 pharmacy compounding prescriptions) and the off-label drug use rate was 38.2% (161 substances; 819 prescriptions). Reasons for off-label drug use included unapproved age group (n=436 [53.2%]), dosing (n=226 [27.6%]), frequency (n=206 [25.2%]), indication (n=45 [5.5%]) and administration route (n=46 [5.6%]). Of the off-label drug prescriptions, 39.3% (n=322) were associated with strong scientific support.
CONCLUSIONS: On a randomly selected day, 8.3% of prescriptions were unlicensed and 38.2% were off-label for children hospitalized at the authors' institution. Of off-label prescriptions, only 39.3% were associated with strong scientific support.

Key Words: *Evidence-based medicine; Off-label use; Paediatrics*

Les médicaments non brevetés ou utilisés dans une indication non autorisée en pédiatrie dans un hôpital mère-enfant de soins tertiaires

OBJECTIF : Évaluer l'emploi des médicaments non brevetés et utilisés dans une indication non autorisée en une seule journée dans un hôpital pédiatrique de soins tertiaires du Canada.
MÉTHODOLOGIE : Des chercheurs ont réalisé une étude transversale dans un hôpital pédiatrique de soins tertiaires au cours d'une journée sélectionnée au hasard. Ils ont analysé les prescriptions actives des enfants de moins de 18 ans. Les médicaments non brevetés désignaient les médicaments non commercialisés au Canada ou commercialisés, mais préparés en pharmacie. Les médicaments utilisés dans une indication non autorisée (MUINA) désignaient les médicaments commercialisés au Canada utilisés dans un groupe d'âge, une indication, une dose, une fréquence ou une voie d'administration non approuvé. Les chercheurs ont analysé les MUINA associés à un solide appui scientifique au moyen du *Pediatric Dosage Handbook, 14th edition* et de Micromedex® Solutions. Ils ont calculé le nombre et la proportion de médicaments non brevetés et de MUINA prescrits, ainsi que celui des MUINA liés à un solide appui scientifique.
RÉSULTATS : Le 5 mars 2014, les chercheurs ont extrait 2 145 prescriptions de médicaments qu'ils ont incluses dans la présente étude. Le taux d'utilisation de médicaments non brevetés s'élevait à 8,3 % (57 produits non brevetés, 75 médicaments non commercialisés et 103 préparations pharmaceutiques) et celui de MUINA, à 38,2 % (161 substances; 819 prescriptions). Les raisons pour lesquelles les prescriptions étaient considérées comme des MUINA étaient un groupe d'âge (n=436 [53,2 %]), une dose (n=226 [27,6 %]), une fréquence (n=206 [25,2 %]), une indication (n=45 [5,5 %]) ou une voie d'administration (n=46 [5,6 %]) non approuvé. Parmi les MUINA, 39,3 % (n=322) étaient liés à un solide appui scientifique.
CONCLUSIONS : Au cours d'une journée sélectionnée au hasard, 8,3 % des prescriptions n'étaient pas brevetées et 38,2 % étaient utilisées dans une indication non autorisée chez les enfants hospitalisés dans l'établissement des auteurs. Parmi les MUINA, seulement 39,3 % étaient liés à un solide appui scientifique.

Unlicensed and off-label drug use in children appears to be a necessity to provide adequate patient care because children remain 'therapeutic orphans' >50 years after Shirkey (1) coined the term. In response to the need for more studies involving children to add to the limited data regarding efficacy and safety, international bodies and governmental health agencies have tightened their regulation and evaluation processes to encourage paediatric studies. For instance, in 2000, the International Conference on Harmonization adopted its E11 chapter, "Clinical Investigation of Medicinal Products in the Pediatric Population" (2).

In the United States (US), the Food and Drug Administration Modernization Act was passed in 1997 to allow financial incentives for pharmaceutical drug manufacturers to conduct paediatric studies, in addition to offering an additional six months of market exclusivity (3), which was followed in 2002 and 2003 by the Best Pharmaceuticals for Children Act (4) and the Pediatric Research Equity Act (5), respectively.

In 2007, Pediatric Regulation came into force in the European Union, with the objective of improving "the health of children by facilitating the development and availability of medicines for children aged 0 to 17 years, ensuring that medicines for use in children are of high quality, ethically researched and authorised appropriately and improving the availability of information on the use of medicines for children" (6).

In Canada, in 2006, an amendment to the Food and Drug Act allowed an extension to the data protection period to be extended

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a further six months if, "results of pediatric clinical trials, designed and conducted for the purpose of increasing knowledge of the use of the drug in pediatric populations, are also submitted and found acceptable" (7). The Pediatric Expert Advisory Committee was formed in 2009; however, Health Canada has no authority to mandate specific drug studies in paediatrics as the Food and Drug Administration and European Medicines Agency have. The major consequences are that, usually, paediatric drug studies are not conducted in Canada and product monographs can be outdated (8).

Therefore, because it is unclear how much progress has been made at the hospital level in terms of unlicensed and off-label drug use, we wanted to describe these uses in a tertiary care paediatric hospital in Canada. Furthermore, there is no recent Canadian data regarding the rate of unlicensed and off-label drug use in the paediatric population.

METHODS

The present retrospective cross-sectional study aimed to determine the unlicensed and off-label drug use rates and the scientific support associated with these uses in a tertiary care paediatric university hospital. Because of its retrospective nature and as per institutional review board guidelines, informed consent was not required and the study was approved by the chief of medical staff.

Health care setting

The present study was conducted in a 500-bed tertiary care paediatric hospital. Clinical pharmacists participate on a daily basis in ward rounds and provide advice on drug prescription, administration and monitoring. The pharmacy department uses a closed drug formulary with the collaboration of a pharmacology and therapeutics committee. The local drug formulary includes 821 drug substances (2045 drug formulations); of these, 66 drug substances are imported through Health Canada's Special Access Program (75 formulations).

Definitions and study variables

Unlicensed drug use was defined as either: the use of nonmarketed drugs in Canada for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, or are unsuitable or unavailable; or the use of nonmarketed formulations of marketed drugs obtained through pharmacy compounding. Reconstituted and repackaged formulations without further compounding were excluded.

Off-label drug use was defined as the use of marketed drugs in Canada for an unapproved age group, indication, dosage, frequency and/or administration route. Off-label status was determined using the Canadian monographs published by drug manufacturers (9,10). For generic drugs, a drug monograph of the current drug manufacturer was considered; if not available, a drug monograph from another generic drug manufacturer was considered. If no mention of "paediatrics" or "children" was included in the drug monograph, the prescription was considered to be off-label. For the unapproved age group, other criteria were considered not applicable. Unapproved indication was confirmed through review of medical progress notes recorded in the medical chart. These notes addressed the specific medical problem the patient was facing and the context in which the drug was prescribed.

However, for antibiotic prescriptions, antibiograms were not reviewed due to their unavailability in the computerized database. Also, specific indications for analgesics, oral contraceptives, laxatives and cardiotropic drugs were not reviewed. Unapproved dosage was defined as a dose 20% greater than the recommended maximal dose to account for dose rounding (11).

Both unlicensed and off-label statuses were evaluated as of April 1, 2014. Unlicensed and off-label drug definitions were considered to be mutually exclusive.

Data extraction

All active paediatric (<18 years of age) inpatient drug prescriptions for the 24 h study period were extracted from the institution's pharmacological information system (CGSI TI Inc, Canada). Outpatient drug prescriptions, including emergency room prescriptions and inpatient drug prescriptions for operating and delivery rooms, were excluded. For each prescription, the following patient and drug data were extracted: patient's date of birth, weight, dates of admission and discharge, generic name of drug, date of drug prescription, and drug dosage, frequency and administration route. If a prescription was modified during the study period, both drug prescriptions were included and analyzed separately. The current Canadian drug status was identified in the hospital's drug purchasing database (GRM Espresso, Logibec Groupe Informatique, Canada).

Data analysis

The unlicensed drug use rate was calculated by dividing the number of unlicensed drug prescriptions by the total number of drug prescriptions. The proportion of unlicensed drug uses for unmarketed drugs and the proportion of marketed drugs with pharmacy compounding were calculated. The off-label drug use rate was calculated by dividing the number of off-label drug prescriptions (at least one unapproved criteria) by the total number of drug prescriptions. The proportions of off-label drug uses per unapproved criteria (eg, age group, indication, dosage, frequency and administration route) were also calculated. For these results, 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 included in each of these off-label categories). The proportion of off-label drug prescriptions associated with strong scientific support in the literature, according to Micromedex® Solutions (12) and Lexicomp's *Pediatric Dosage Handbook, 14th edition* (13), was calculated. Both databases were relevant because they contain consistent information regarding drug uses in paediatrics and are used daily by clinical pharmacists at the authors' institution. An off-label drug prescription was considered to have strong scientific support if sufficient information to justify the use of the drug for all unapproved criteria could be retrieved.

RESULTS

A total of 2145 drug prescriptions for children <18 years of age were extracted on Wednesday, March 5, 2014, for 308 inpatients; mean patient age was 10.9 years (range zero to 18 years). Of these prescriptions, 609 were for adolescents (≥12 to 18 years of age), 764 for children (2 to 12 years of age), 445 for infants (28 days to <2 years of age) and 327 for newborns (<28 days of age).

Of the 2145 drug prescriptions included, the 10 most prescribed drugs represented 32.1% (n=689) of all drug prescriptions: acetaminophen (n=206), cholecalciferol (n=73), sucrose (n=71), dimenhydrinate (n=71), morphine sulfate (n=54), salbutamol (n=46), lansoprazole (n=46), polyethyleneglycol (n=43), iron (n=41) and heparin (n=40). A total of 319 different drugs were prescribed.

The overall unlicensed drug use rate was 8.3% (n=178) of all prescriptions. Infants had the highest rate of unlicensed drug use (12.1%) and 57 different unlicensed drug products were prescribed; 42% (n=75) of prescriptions were for nonmarketed drugs and 58% (n=103) were for marketed drugs with pharmacy compounding.

TABLE 1
Reason for unapproved use of the 20 most frequent off-label drug prescriptions

Drug	Prescriptions, n	Off-label	Reason for unapproved use*					Strong scientific support†
			Age	Indication	Dosage	Frequency	Route of administration	
Morphine sulfate	54	54 (100)	54 (100)	NA	NA	NA	NA	39 (72.2)
Salbutamol	46	43 (93.5)	25 (58.1)	0 (0)	12 (27.9)	18 (41.8)	0 (0)	12 (27.9)
Polyethylene glycol 3350	43	42 (97.7)	42 (100)	NA	NA	NA	NA	42 (100)
Lansoprazole	44	40 (90.9)	10 (25.0)	26 (65.0)	2 (5.0)	9 (22.5)	2 (5.0)	2 (5.0)
Diphenhydramine	40	23 (57.5)	4 (17.4)	0 (0)	17 (73.9)	6 (26.1)	0 (0)	1 (4.3)
Dimenhydrinate	71	22 (40.0)	2 (9.1)	0 (0)	14 (63.6)	8 (36.4)	1 (4.5)	0 (0)
Piperacilline + tazobactam	22	20 (90.9)	20 (100)	NA	NA	NA	NA	19 (95.0)
Ondansetron	23	19 (82.6)	2 (10.5)	0 (0)	4 (21.1)	16 (84.2)	0 (0)	0 (0)
Metoclopramide	20	18 (90.0)	0 (0)	0 (0)	8 (44.4)	18 (100)	0 (0)	3 (16.7)
Hydrocortisone	28	18 (64.3)	0 (0)	0 (0)	17 (94.4)	18 (100)	0 (0)	9 (50.0)
Fentanyl	17	17 (100)	15 (88.2)	0 (0)	0 (0)	2 (11.8)	0 (0)	8 (47.0)
Ranitidine	19	16 (84.2)	16 (100)	NA	NA	NA	NA	11 (68.8)
Furosemide	20	16 (80.0)	0 (0)	0 (0)	12 (75.0)	6 (37.5)	1 (6.3)	2 (12.5)
Acetaminophen	206	15 (7.3)	0 (0)	0 (0)	7 (46.7)	0 (0)	8 (53.3)	0 (0)
Lorazepam	18	15 (83.3)	15 (100)	NA	NA	NA	NA	8 (53.3)
Hydromorphone	29	14 (48.3)	14 (100)	NA	NA	NA	NA	7 (50.0)
Pentamidine	14	14 (100)	14 (100)	NA	NA	NA	NA	7 (50.0)
Midazolam	16	14 (87.5)	14 (100)	NA	NA	NA	NA	13 (92.9)
Trimethoprim + sulfamethozaxol	23	11 (47.8)	1 (9.1)	0 (0)	4 (36.4)	8 (72.7)	1 (9.1)	3 (27.3)
Nystatin	13	10 (76.9)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	3 (30.0)

*Data presented as n (%) unless otherwise indicated. *Off-label drug use was defined as the use of marketed drugs in Canada for an unapproved age group, indication, dosage, frequency and/or administration route. †An off-label drug prescription was considered to have strong scientific support if sufficient information could be retrieved to justify the use of the drug for all unapproved criteria. NA Nonapplicable (if the age group was unapproved, other criteria were non-applicable)*

The overall off-label drug use rate was 38.2% (n=819). Children had the highest rate of off-label drug use (48.4%) and 161 different off-label drug products were prescribed. The reasons for off-label use were mainly unapproved age (n=436 [53.2%]), dosing (n=226 [26.7%]), frequency (n=206 [25.2%]), route of administration (n=46 [5.6%]) and indication (n=45 [5.5%]). Additionally, 39.3% (n=322) of off-label prescriptions were associated with strong scientific support. The top 20 off-label drug substances prescribed are presented in Table 1.

DISCUSSION

The present study revealed a rate of 8.3% for unlicensed drug prescriptions and a rate of 38.2% for off-label drug prescriptions in children hospitalized in a tertiary care paediatric hospital on a randomly selected day in 2014.

Unlicensed drug prescriptions

In seven studies published between 2000 and 2014, the rate of unlicensed drug prescriptions in paediatric inpatients varied between 0.2% and 36% (14-20). Many reasons explain the continuous need for unlicensed drug use, notwithstanding the initiatives to encourage paediatric clinical research.

Drugs are not equally available in all countries because drug manufacturers are not required to submit a drug for sale in every country, although they will usually strive to satisfy national regulatory processes to gain market access in several countries. While Health Canada provides a Notice of Compliance database to identify drugs that can be marketed in Canada, there is no public list of pending and rejected drug submissions. For instance, etomidate has been used as an unlicensed drug for >20 years in Canada while it has been commercialized in the US since 1996.

Drug shortages also compel the use of unlicensed drugs. In fact, Canada has experienced an unprecedented drug shortage crisis in the past three years. Health Canada only considers authorizing a Special Access Program drug for use if no other alternative is available (21). However, to resolve a drug shortage, hospitals can be required to import an unlicensed drug themselves.

Finally, the unavailability of paediatric oral liquid formulations is certainly a key factor in explaining the use of unlicensed drugs in paediatric hospitals. In our study, at least 45 drugs were considered unlicensed because pharmacy staff had to compound a formulation suitable for children.

Off-label drug prescriptions

In eight studies published between 2000 and 2014, the rate of off-label drug prescriptions in paediatric inpatients varied from 18% to 66% (14-20,22). The evaluation of off-label drug use rates is more complex than that of unlicensed drug use rates. First, it requires a medical chart review to identify indications for drug prescription. Second, the classification of a drug prescription as on- or off-label will depend on the gold standards selected for comparison (eg, drug monographs, scientific databases, books).

Our study indicates that 38.2% (n=819) of all drug prescriptions audited on a single day were off-label and were unapproved for age group (53.2%), indication (5.5%), dosage (27.6%), frequency (25.2%) and administration route (5.6%).

In the US, Olsson et al (23) reported in 2011 that 74.5% of drug prescriptions in children are off-label because there is no paediatric information in the drug monograph. In 2013, Ballard et al (24) reported the following reasons for off-label drug use: unapproved drug dosage or drug frequency (13.1% of prescriptions); unapproved age range or patient weight (10.6%); unapproved indication (9.5%); and unapproved route of administration (<1%). In 2013, Lee et al (25) reported the following reasons for off-label drug use: absence of paediatric information (22.4%); unapproved indication (22.4%); unapproved age group (37.6%); unapproved route of administration (1.2%); unapproved

drug dosage (9.4%); and unapproved drug frequency (7.0%). In Canada, Eguale et al (26) reported in 2012 that the prevalence of off-label drug prescriptions in primary care was 11% of outpatients.

In a guidance document for the industry, Health Canada states:

> for indications approved for adults in general, a statement regarding use in the pediatric population should be included. The term pediatric generally pertains to persons between birth and 16 years of age, (…), therefore the Pediatric subtitle should include the age upon which the pediatric recommendation is based. (27)

This issue is crucial for clinicians. In 2014, the Council of Canadian Academies published a report on the improvement of medicines for children in Canada. The report identified key issues surrounding the lack of medicines available for children (8). The report suggests that medications must be studied in children and formulated for them because they also take these medications and respond to them differently than adults. Furthermore, studying medications in children is possible and in their best interest. Finally, Canada should follow the US and European Union's examples and implement Pediatric Regulation.

Evidence supporting off-label use

Using a drug off-label can be a necessity if the drug industry has not pursued paediatric research for market approval. Clinicians treating children are confronted with the necessity of prescribing drugs using their clinical judgment and the scarce available literature. In our study, only 39.3% of all off-label drug prescriptions evaluated were supported by strong scientific evidence. Similarly, in the US in 2006, Radley et al (28) found that 73% of off-label uses were not evidence-based. In Canada in 2012, Eguale et al (26) found that 79% of off-label prescriptions lacked strong scientific evidence. While these studies highlighted a similar lack of supporting evidence, the authors used different gold standards to assess this evidence. In the study by Radley et al (28), the authors compared prescriptions using Micromedex® (12). In the study by Eguale et al (26), drug use was considered evidence-based if the following three criteria were met:

> (1) the drug is effective or favors efficacy for a particular treatment indication, (2) the drug is recommended for most or all patients with the treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence included at least 1 [randomized clinical trial] RCT.

These results suggest that, considering the lack of paediatric clinical research, clinicians must use drugs without strong scientific support to treat patients with refractory or complex conditions.

Limitations

The drug prescription sample used represents a single day in the year and some drugs' uses can vary significantly during the year because of the seasonality of medical conditions, especially respiratory tract infections or trauma. For off-label uses, treating physicians were not contacted to obtain further information concerning the indications of the drugs they prescribed. However, in the vast majority of cases, indications were clear from the chart review process and there are no reasons to suspect that there may be a difference between on- or off-label drug uses. Furthermore, in the present study, we did not investigate accidents and adverse drug events associated with the use of unlicensed and off-label drugs. Further studies are required to document costs, delays and adverse events associated with unlicensed and off-label drug uses inside and outside the hospital.

CONCLUSION

The present study adds to the existing literature regarding unlicensed and off-label drug uses in children. Furthermore, we evaluated scientific support associated with these uses and this information is crucial for clinicians. Our study showed an unlicensed drug use rate of 8.3%. Most unlicensed drug substances were marketed drugs that required pharmacy compounding. The off-label drug use rate was 38.2%. Reasons for off-label drug use were unapproved age range (53.2%), indication (5.5%), dosing (27.6%), frequency (25.2%) and route of administration (5.6%). Thirty-nine percent of off-label drug uses had strong scientific support. These results are similar to previously published research. Further studies are required to document costs, delays and adverse events associated with unlicensed and off-label drug uses. At our centre, the use of unlicensed and off-label drugs in children will become an annual audit measure included in our risk analysis program. Such trending may contribute to reconsider current clinical practices.

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