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Off-label and unlicensed drug use in a pediatric intensive care unit of a tertiary care Spanish hospital. A descriptive study

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ABSTRACT

Introduction. In pediatric intensive care units, a large number of drugs are used, many of which are prescribed for condition beyond those established in their summary of product characteristics (off-label and unlicensed drug prescriptions). The objective of this study was to describe drug use and estimate the prevalence of off-label and unlicensed drugs in a pediatric intensive care unit of a tertiary care Spanish hospital.

Population and methods. Cross-sectional, observational study with a single cohort of children admitted to a pediatric intensive care unit. The study was conducted in 2017. Each drug prescription, its conditions of use and administration were reviewed. In addition, the summary of product characteristics of drugs used were analyzed in order to identify whether they were used according to their conditions of authorization, or whether they were used in an off-label or unlicensed manner.

Results. The sample included 97 patients. At least one off-label or unlicensed drug was administered to 74.2% (n = 72) of patients; 23.8% (n = 243) corresponded to off-label prescriptions and 8.7% (n = 89), unlicensed prescriptions. A sub-analysis by age group showed that the age group that received a higher number of total prescriptions (n = 611) and a higher percentage of off-label and/or unlicensed drug prescriptions (38.4%) was under 2 years of age.

Conclusions. Off-label and/or unlicensed drug prescription is a common practice in the pediatric intensive care unit. This study allowed us to document the complexity of therapeutics in children.

Key words: *pediatric intensive care units, off-label use, child, prescriptions.*

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INTRODUCTION

Several physiological and developmental characteristics in the pediatric population are very different from those of adults. It is a heterogeneous group, whose pharmacokinetics and pharmacodynamics vary depending on the age range.[1,2] While in the adult population, drugs whose safety and effectiveness have been demonstrated in clinical trials are generally used, health care providers in pediatric areas are forced to handle drugs that have not been specifically studied in children, making adjustments according to their weight and/or body surface area.[3] The same data are not available for the pediatric population due to a series of well-known obstacles that limit clinical research to assess the use of drugs in this population[4,5] (the limited commercial interest of pharmaceutical companies in this age group and the ethical and methodological difficulties involved in research in this group).[6] Thus, many drugs have not been studied specifically in children and have a limited level of evidence.[6,7] The lack of data about children in the summary of product characteristics (SPCs) forces the prescription of drugs under conditions other than those specified in the SPCs,[8] a practice that entails risks,[9] such as an increased incidence and severity of adverse reactions warned by the European Medicines Agency (EMA).[10]

The SPCs is a collection of scientifically proven information on medicines for health care providers.[11] When drugs are used outside the framework defined in the SPCs, it is referred to as off-label (OL) use.[12] Among the most common reasons used to classify a prescription as OL[13] we have prescriptions for an indication, age range, dosage and/or route of administration that is different from those stated in the drug's authorization document.

Another situation of special drug use motivated by the lack of development of pediatric drugs is that internationally identified as unlicensed (UL) use, a broad, heterogeneous, and sometimes ambiguous term under which different authors[12–16] have classified foreign drugs, drugs that have to be manipulated (crushed, dissolved in water, concentrated or diluted more than what is authorized in the SPCs) for their administration, and compounded preparations.

Although there is currently an extensive list of effective, safe, and cost-effective drugs included in the list of essential medicines for children[17] of the World Health Organization (WHO) and an effort by regulatory agencies to increase research in this population, drugs continue to be prescribed outside the conditions established in their SPCs.[18]

Focusing on the setting of pediatric intensive care units (PICUs), there is extensive exposure of patients to drugs, many of which correspond to OL and UL use[6,19] despite the increasingly common initiatives taken worldwide to improve this practice.[20] Therefore, the objective of this study was to describe drug use in a PICU and to estimate the prevalence of OL and UL drug use.

POPULATION AND METHODS

A cross-sectional, observational study with retrospective data collection was conducted at the PICU of Hospital 12 de Octubre in Madrid, Spain, in 2017. The PICU had 16 beds and the patients' medical records consisted of both electronic (medical prescription) and paper (nursing notes) records.

The medical records of patients aged 1 month to 14 years admitted to the PICU between January 1st and December 31st, 2016 were included, regardless of their origin and/or disease. Incomplete medical records were excluded.

The sample size was estimated taking into account the proportion of patients admitted to the PICU receiving at least one OL drug described by the reviewed bibliography[6] (89%); an alpha error of 5%, a precision of +/-7%, and a potential loss of 30% were defined (GRANMO V7.12, April 2012). A total of 110 patients were considered.

The medical records analyzed in this study were randomly selected from all PICU admissions occurred during the study period. The following variables were obtained from the medical records: age, sex, weight, reason for admission, length of stay, name of the drug prescribed by active ingredient, ATC code[21] (Anatomical, Therapeutic, Chemical Classification System), indication, age of the specific indication, dosage (dose and interval), and route of administration for each prescription.

For the study, data were collected and analyzed since the date of admission to the date of discharge of each patient. A new prescription was considered when the drug, route of administration, pharmaceutical form and/or dosage of each active ingredient was modified.

The information available in the SPCs published in the Medicine Online Information Center (*Centro de Información online de Medicamentos*, CIMA)[22] of the Spanish Agency of Medicines and Medical Devices was also reviewed for each drug prescription. According

to the information contained in the SPCs, prescriptions were classified into on-label (ON) prescriptions (those made according to the SPCs information), off-label (OL) prescriptions[13] (those made for a different indication, dosage, age range and/or route of administration from those indicated in the official drug authorization document), and unlicensed (UL) prescriptions (UL) (drugs that are not licensed in Spain, compounded preparations, and drugs that required manipulation for their administration).

Statistical analysis

A descriptive analysis was performed; thus, qualitative variables are described as absolute and relative frequency (percentage). The normality of quantitative variables was analyzed using the Kolmogorov-Smirnov statistical test, and it was observed that they did not fit the normal distribution (p value < 0.05); therefore, the central tendency of these variables was expressed using the median and the dispersion, using the interquartile range (IQR).

For the statistical analysis, the SPSS® version 20.0 software package (SPSS Science, Chicago, Illinois, USA) was used.

Ethical considerations

Data were accessed in accordance with the hospital protocols and after obtaining the consent and approval of the Research Commission and the site's Ethics Committee (registration number: TP17/0058). It was not necessary to request an informed consent from patients because this was a retrospective study with review of anonymized medical records.

RESULTS

Between January 1st and December 31st, 2016, 139 children were admitted to the PICU of Hospital 12 de Octubre. A total of 110 medical records were reviewed for the study; 13 were excluded due to lack of relevant data. The final sample was made up of 97 patients, whose median (IQR) age was 20.0 (65) months, 53.6% (n = 52, 95% confidence interval [CI]: 43.3–63.9)

Table 1. Patient characteristics (n = 97)

	Number of patients (%)	95% CI	Median and IQR
Age			20.0 (65.0)
≤ 2 years	58 (59.8)	49.5–70.1	
2–4 years	8 (8.2)	3.1–14.4	
4–6 years	8 (8.2)	3.1–14.4	
6–8 years	5 (5.2)	1.0–10.3	
8–10 years	3 (3.1)	0.0–7.2	
10-12 years	4 (4.1)	1.0-8.2	
12-14 years	11 (11.3)	4.2-18.6	
Sex			
Male	52 (53.6)	43.3–63.9	
Female	45 (46.4)	36.1–56.7	
Type of patient			
Medical	63 (64.9)	55.7–75.3	
Surgical	34 (35.1)	24.7–44.3	
Weight (kg)			10.4 (17.5)
Days of hospitalization			2.0 (3.5)
Body organ system and health condition associated with admission			
Reconstructive/other surgery	34 (35.1)	3.1–85.8	
Cardiovascular system	20 (20.6)	0.0–44.5	
Respiratory system	12 (12.4)	1.0–28.8	
Nervous system	11 (11.3)	0.0–32.0	
Trauma injuries	6 (6.2)	0.0–14.4	
Other	6 (6.2)	0.0–19.6	
Infectious diseases	4 (4.1)	0.0–11.4	
Blood disorders	3 (3.1)	0.0–6.3	
Endocrine disorders	1 (1.0)	0.0–3.1	

Patient characteristics are expressed as number of patients (values between parentheses indicate percentages), confidence interval for categorical variables (95% CI), median, and interquartile range (IQR) since this is a sample with a non-normal distribution.

were males. The youngest subject was 1 month old and the oldest, 168 months (14 years). Males' median age was 12.5 (51.0) months, whereas females' median age was 24.0 (117.5) months. Also, 59.8% (n = 58, 95% CI: 49.5–70.1) of the sample consisted of children younger than 24 months. The median length of stay was 2.0 (3.5) days.

The main characteristics of the patients and the reasons for admission can be found in *Table 1*.

During their hospital stay, the 97 patients received a total of 1017 drug prescriptions for a total of 143 different active ingredients. The median number of drugs prescribed per patient was 8 (7.5). The patient in whom the most drugs were prescribed received 43 drugs and the one with the least drugs prescribed received 1.

Of the 1017 prescriptions, 685 (67.4%) were ON, 243 (23.9%) were OL, and 89 (8.8%) UL. The total percentage of prescriptions that did not follow the information contained in the drug's SPCs (OL+UL) was 32.6% (n = 332). The median number of drugs prescribed per patient that were ON was 6.0 (4.0); OL, 1.0 (4.0); and UL, 0.0 (1.0).

The data showed that 25.8% (n = 25) of the sample received all their prescriptions ON, while 74.2% (n = 72) of the patients received at least 1 drug under different conditions. Seventy patients (72.2%) received at least 1 OL prescription and 34 (35.1%), at least 1 UL prescription (*Tables 2* and *3*).

The sub-analysis by age group showed that the age group that received a higher number of prescriptions in total, as well as a higher percentage of OL/UL prescriptions, was children under 2 years of age (*Table 3*).

Some of the drugs most frequently prescribed as OL use were dopamine (n = 24, 100%), pantoprazole (n = 15, 100%), and phytonadione (n = 15, 88.2%). Under UL conditions: furosemide (n = 15, 33.3%), diazepam (n = 9, 100%), and captopril (n = 8, 100%).

The most frequent reasons for OL use in this study were age and indication. Intravenous dopamine, pantoprazole, levetiracetam, and levosimendan were prescribed in 100% of cases as OL for age. In all of these cases, according to the SPCs, these drugs were not indicated for the pediatric population in general. Lastly, in the case of intravenous milrinone, it was prescribed in 71.4% (n = 10) of the OL use for an indication and dosage different from those indicated in its SPCs.

The most frequent causes for UL drug use were the fact that it was a foreign drug or a compounded preparation prepared and provided by the hospital's pharmacy department.

Ranitidine, methadone, spironolactone, and hydrochlorothiazide were used in UL prescriptions (as liquid compounded preparation); furosemide and captopril were administered as tablets even at ages where tablet ingestion is not possible (10 patients younger than 24 months received furosemide and 5, captopril). There were no records on whether or not a drug was manipulated for administration. *Table 4* shows the reasons for OL and UL prescriptions.

DISCUSSION

Different authors have explored OL and UL drug use so far, and frequencies between 36%[23] and 57%[6] have been described; these figures exhibit ample and interpretable differences because drug marketing and SPCs contents may vary among different countries.

The estimated frequency of OL and UL drug prescriptions in this study (32.6%) differs from similar studies conducted in our country: Blanco-Reina[6] identified 57%; García-López,[19] 62.5%; and Saldaña-Valderas,[24] 46%. The main difference may be attributed to the fact that these studies included neonatal patients in their sample and the higher percentages of OL and UL drug prescriptions tend to occur in the younger age groups.[19,23,25] There appears to be a linear relationship between the frequency of OL and UL drug use and the patient's age: frequency increases as patient's age decreases.[26] It is worth remembering that, as the patient's age decreases, developing research becomes more complicated and, therefore, so does the possibility of obtaining data to bolster drug SPCs.[5] This may be the reason why the number of patients receiving at least 1 OL drug detected in our population (72.1%) is lower than that estimated by other authors (89%[6] and 96%[24]).

The percentage of UL drug use found in our sample (8.7%) is very similar to that observed in other national studies,[6,19] but is well below that of studies carried out in other countries, such as India[25] (21.0%) or Malaysia[26] (27.3%). It is important to take into account that no records were found on the manipulation of drugs to enable their administration in children, a fact that could increase the percentage of this type of drug use. Although there were no records on the manipulation of furosemide and captopril, they were all prescribed as tablets, so they had to be

Table 2. Drugs prescribed at the PICU by ATC group and within each category of use: on-label (ON), off-label (OL), and unlicensed (UL)

ACTIVE INGREDIENT	ATC GROUP	PRESCRIPTIONS N (%)	ON %	OL %	UL %
Nervous system	**GROUP N**	**333 (32.7)**			
ACETAMINOPHEN	N02BE01	91	100	0	0
METAMIZOLE	N02BB02	72	94.4	5.5	0
MORPHINE	N02AA01	46	100	0	0
MIDAZOLAM	N05CD08	37	81.0	18.9	0
FENTANYL	N01AH01	24	45.8	54.1	0
LORAZEPAM	N05B	12	100	0	0
REMIFENTANIL	N01AH06	11	45.4	54.5	0
LEVETIRACETAM	N03AX14	10	0	100	0
DIAZEPAM	N05BA01	9	0	0	100
PROPOFOL	N01AX10	8	100	0	0
METHADONE	N07BC02	8	0	0	100
SEVOFLURANE	N01AB08	5	100	0	0
Antiinfectives for systemic use	**GROUP J**	**145 (14.3)**			
CEFAZOLINE	J01DB	30	56.5	43.3	0
VANCOMYCIN	J01XA01	21	90.4	9.5	0
AMOXICILLIN-CLAVULANIC ACID	J01CR02	20	100	0	0
AMPICILLIN	J01CA01	14	100	0	0
CEFOTAXIME	J01DD01	13	100	0	0
GENTAMICIN	J01GB03	11	100	0	0
PIPERACILLIN-TAZOBACTAM	J01CR05	9	88.8	11.1	0
METRONIDAZOLE	J01XD	9	100	0	0
MEROPENEM	J01DH02	8	75	25	0
CLINDAMYCIN	J01FF01	5	100	0	0
FLUCONAZOLE	J02AC01	5	100	0	0
Cardiovascular system	**GROUP C**	**133 (13.1)**			
FUROSEMIDE	C03CA01	45	66.6	0	33.3
DOPAMINE	C01CA04	24	0	100	0
MILRINONE	C01CE02	14	28.5	71.4	0
NORADRENALINE	C01CA03	11	100	0	0
CAPTOPRIL	C09AA01	8	0	0	100
SPIRONOLACTONE	C03DA01	7	0	0	100
EPINEPHRINE	C01CA24	6	100	0	0
HYDROCHLOROTHIAZIDE	C07BB07	6	0	0	100
LEVOSIMENDAN	C01CX08	6	0	100	0
URAPIDIL	C02CA06	6	66.6	33.3	0
Alimentary tract and metabolism	**GROUP A**	**132 (13.0)**			
RANITIDINE	A02BA02	71	71.8	19.7	8.4
ONDANSETRON	A04AA01	37	100	0	0
PANTOPRAZOLE	A02BC02	16	0	100	0
HUMAN INSULIN	A01AB01	9	100	0	0
Systemic hormonal preparations, excluding sex hormones and insulins	**GROUP H**	**40 (3.9)**			
METHYLPREDNISOLONE	H02AB04	19	100	0	0
DEXAMETHASONE	H02AB02	16	68.7	31.2	0
HYDROCORTISONE	H02AB09	5	100	0	0
Respiratory system	**GROUP R**	**20 (2.0)**			
SALBUTAMOL	R03AC02	10	50	50	0
IPRATROPIUM BROMIDE	R03BB01	5	100	0	0
DEXCHLORPHENIRAMINE	R06AB02	5	20	80	0
Blood and blood forming organs	**GROUP B**	**17 (1.7)**			
PHYTONADIONE	B02BA01	17	11.7	88.2	0
Musculo-skeletal system	**GROUP M**	**11 (1.0)**			
ROCURONIUM	M03AC09	11	54.5	45.5	0
Other with < 5 prescriptions		**186 (18.3)**	51.8	31.1	10.7
TOTAL		**1017**			

broken, crushed and/or dissolved in order to be ingested by children, especially by the youngest ones. For example, the SPCs for furosemide[27] states that it should be swallowed with water and without chewing; modifying the administration in this sense will change the drug absorption and may cause it to be absorbed faster and/or in larger amounts, with a potential variation in the expected effect (onset and magnitude). A similar thing occurs with captopril,[28] with the addition that its safety and effectiveness have not been established in children.

An aspect in which we found notable differences in relation to other studies is the reason why the drug was used in OL conditions. In similar studies, the dose was the main reason for classifying the prescription as OL,[6,23,29] whereas the main cause in our study was the age at which these drugs were used. Such difference may be due to the inequalities in drug therapies dependent on geographic areas discussed before.

The updates of reviewed SPCs dated from years prior to 2015. This may lead to some of the OL or UL uses described in this article not being considered as such in daily clinical practice, because, sometimes, the experience with a drug is introduced in the clinical guidelines but, however, this information is not reflected in the drug SPCs because it has not been collected by means of regulated research and/or by the laboratory responsible for marketing it. This fact corroborates the need to assess drug use in children by conducting clinical trials with drugs in the pediatric population.[30]

The main limitation of this study is its retrospective design which includes data obtained from the medical records and this could have resulted in a loss of information. Therefore, patients whose records did not include the variables predefined in this study were considered losses.

A strength of this study is that it provides valuable information on the use of drugs in a PICU, especially in relation to OL and UL use. This information may broaden knowledge about prescriptions in the critically ill pediatric population and increase awareness of the safe and effective use of drugs.

CONCLUSION

In our sample, we found a 32.6% prevalence of OL and UL drug use. Despite the great effort to develop drugs for children, OL and UL prescriptions are still frequent, and there is still a lack of clear data about their safety and effectiveness, as well as their description in SPCs. ■

Table 3. Summary of statistical parameters analyzed for prescriptions

	Total	ON	OL	UL	OL + UL
	N (%)	N (%)	N (%)	N (%)	N
Patients with prescriptions	97	25	70	34	*72
	(100)	(25.8)	(72.2)	(35.1)	(74.2)
Prescriptions	1017	685	243	89	89
	(100)	(67.4)	(23.9)	(8.8)	(32.6)
Prescriptions per patient	8 (7.5)	6 (4.0)	1 (4.0)	0 (1.0)	1 (5.0)
Median and IQR					
Prescriptions by age group					
≤ 24 months	611 (60.1)	376 (61.5)	173 (28.3)	62 (10.1)	235 (38.4)
2–4 years	75 (7.4)	57 (76.0)	12 (16.0)	6 (8.0)	18 (24)
4–6 years	98 (9.6)	63 (64.3)	21 (21.4)	14 (14.3)	35 (35.7)
6–8 years	61 (5.9)	49 (80.3)	9 (14.8)	3 (4.9)	12 (19.7)
8–10 years	27 (2.7)	24 (88.9)	3 (11.1)	0 (0.0)	3 (11.1)
10–12 years	65 (6.4)	53 (81.5)	9 (13.8)	3 (4.6)	12 (18.4)
12–14 years	80 (7.9)	64 (80.0)	15 (18.8)	1 (12.5)	16 (31.3)

Prescription characteristics are expressed as number of prescriptions (values between parentheses indicate percentages), median, and interquartile range (IQR) since this is a sample with a non-normal distribution.
** Number of patients in whom at least one drug was used in an off-label and/or unlicensed manner (OL and/or UL).*
ON: on-label use; OL: off-label use; UL: unlicensed use.

Table 4. Reasons for off-label and unlicensed use at the PICU

Use condition	Drugs	Total number of prescriptions	%*	Reason for off-label and unlicensed use
Off-label				
	Dopamine	24	100	Age
	Pantoprazole	15	100	Age
	Phytonadione	15	88.2	Age
	Ranitidine	14	19.7	Indication and age
	Cefazoline	13	43.3	Age
	Fentanyl	11	45.8	Age
	Milrinone	10	71.4	Indication and dose
	Levetiracetam	10	100	Age
	Midazolam	7	18.9	Age
	Remifentanil	6	51.5	Age
	Levosimendan	6	100	Indication
	Rocuronium	5	45.5	Age
	Salbutamol	5	50	Age
	Dexamethasone	5	31.2	Age
	Metamizole	4	5.5	Age
	Dexchlorpheniramine	4	80	Age
	Meropenem	2	25	Age
	Urapidil	2	33.3	Age
	Vancomycin	2	9.5	Dose
	Piperacillin-tazobactam	1	11.1	Dose
Unlicensed				
	Furosemide	15	33.3	Compounded preparation
	Diazepam	9	100	Compounded preparation
	Methadone	8	100	Compounded preparation
	Captopril	8	100	Compounded preparation
	Spironolactone	7	100	Compounded preparation
	Hydrochlorothiazide	6	100	Compounded preparation
	Ranitidine	6	8.4	Compounded preparation
	Sodium phenylacetate and sodium benzoate	1	100	Foreign drug
	Clonidine	2	100	Foreign drug
	Tetracosactide	1	100	Foreign drug
	Ubidecarenone	1	100	Foreign drug

**It indicates the percentage of off-label and unlicensed prescriptions over the total number of prescriptions for each drug.*

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