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Article

Use of unlicensed and off-label drugs in neonates in a Brazilian university hospital

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This study was designed to investigate the use of off-label and unlicensed drugs in a Neonatal Care Unit (NCU) and to compare the frequency of use of off-label drugs according to the drug regulatory agencies in Brazil (Agência Nacional de Vigilância Sanitária-ANVISA) and the United States Food and Drug Administration (FDA). A prospective observational study was carried out in the NCU. Prescriptions were classified as off-label and unlicensed using both ANVISA and FDA criteria. A total of 157 newborns and 1187 prescriptions were analyzed. The most prescribed drug was fentanyl (9.3%), followed by multivitamin (8.4%) and gentamicin (7.9%). According to ANVISA criteria, there were 665 (56.0%) off-label prescriptions and 86 (7.2%) unlicensed prescriptions and 95.5% of newborns received at least one drug off-label. By contrast, according to FDA criteria, there were 592 (49.9%) off-label prescriptions and 84 (7.1%) unlicensed prescriptions, and 72.0% of newborns received at least one drug off-label. The off-label use of drugs registered by ANVISA differed significantly from that of drugs registered by the FDA. There was a high frequency of off-label and unlicensed drug use in the investigated NCU, and there was an inverse relationship between off-label and unlicensed usage and the gestational age of the newborns.

Keywords: Drugs/use/University Hospital/Brazil. Drug/use/off-label/unlicensed. Drug therapy. Neonatology. University Hospital/Brazil.

INTRODUCTION

Pediatric newborns are excluded from clinical trials because of ethical and methodological factors, which include difficulties in conducting clinical trials because of ethical issues, the small number of specialists in pediatric pharmacology, difficulties in the development of pediatric formulations, and low financial returns for the pharmaceutical industry (Dell'Aera *et al.*, 2007; Cuzzolin, Atzei, Fanos, 2006).

The lack of participation of children in clinical research studies is most evident during analyses of the use of drugs in neonates. The scarce number of clinical trials that involve neonates is a consequence of scientific and regulatory challenges, but investigating drugs in neonates is critical (Davis, Connor, Wood, 2012; Dell'Aera *et al.,* 2007; Cuzzolin, Atzei, Fanos, 2006).

There is little evidence on the safety and effectiveness of drugs used in neonates, especially in preterm infants. Over 90% of commercially available drugs have not been approved by the United States Food and Drug Administration (FDA) for use in neonates. Furthermore, appropriate formulations for use in neonates may not exist (Davis, Connor, Wood, 2012).

This scenario leads to the off-label use of drugs, namely the use of drugs with a dose, age, or route of administration that is different from those described on the drug label (Carvalho *et al.*, 2012; Neubert *et al.*, 2010; Carvalho *et al*., 2003). It is also a common practice to use unlicensed medicines that encompass one or more of the following situations: modification of the drug dosage form for medicines registered in a sanitary agency, drug compounding, direct use of chemically pure substances as a medicine, and the use of medicines not yet registered in this country, but that are available through importation (Neubert *et al.*, 2010, O'Donnell, Stone, Morley, 2002).

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A systematic review of studies about the use of medications in children revealed that the frequency of unlicensed and off-label drug use in neonatal units was higher than that in pediatric units (Pandolfini, Bonati, 2005). The percentage of neonates who were exposed to at least one off-label or unlicensed drug ranged from 70.0% to 97.0% in published studies from several countries (De Souza *et al.*, 2016; Lass *et al.*, 2011; Neubert *et al.*, 2010; O'Donnell, Stone, Morle, 2002).

In Brazil, studies published about the use of off-label and unlicensed drugs in neonatology showed a high prevalence of this practice (De Souza *et al.*, 2016; Carvalho *et al.*, 2012). The off-label use in one study was analyzed only considering information included in the FDA registration of drugs (Carvalho *et al.*, 2012). Another study was based on the British National Formulary for Children and Drugdex Micromedex™ (De Souza *et al*, 2016). The off-label use of drugs for use in neonatology was not evaluated using ANVISA as a source of information in any study that was carried out in Brazil.

In this present study, we investigated the use of off-label and unlicensed drugs in a neonatal intensive care unit and compared the frequency of off-label and unlicensed drug use according to the drug regulatory agency in Brazil (National Health Surveillance Agency-ANVISA) and FDA in the United States.

METHODS

Study design and participants

This prospective study was conducted at the neonatal care unit (NCU) of a university hospital in Brazil between January and June 2012. Newborn monitoring occurred throughout the entire hospitalization period. The NCU was located in a teaching hospital that specializes in the treatment of newborns from high-risk pregnancies. The hospital had a total installed capacity of 467 beds, including 24 that were in the NCU. The NCU was a neonatal unit of intensive care type B, as there were no restrictions on the use of mechanical ventilation or provision of assistance to patients undergoing major surgery (Vermont Oxford Network, 2009).

The study included all newborns admitted to the NCU during the investigation period for more than 24 h hospitalization, who were prescribed at least one drug during the hospitalization period, and whose parents and/or legal guardians signed an informed consent form. Newborns who remained in the NCU for less than 24 h and whose parents and/or legal guardian did not agree to participate in the study were excluded. This study was approved by the University Ethics Research Committee (approval number CAAE–0292.0.203.000-11).

Data collection

Perinatal and demographic information for the neonates was obtained from medical records. Newborns were classified as preterm (<37 weeks) or term (≥37 weeks) according to their gestational age. The preterm group was further subdivided into extremely preterm infants (gestational age <28 weeks), very preterm (gestational age of 28–30 weeks), late preterm (gestational age of 31–33 weeks), and preterm (gestational age of 34–36 weeks) (Neubert *et al.*, 2010). The birth weight variable was categorized as either non-low birth weight (≥2500 g) or low birth weight (≤2499 g). The low birth weight group was further subdivided into low birth weight (2499–1500 g), very low birth weight (1499 to 1000 g), and extremely low birth weight (<1000 g) (Ho, 1997).

Study prescription refers to each drug that was prescribed along with its respective daily dose, number of doses per day, and route of administration; these data were collected from prescription charts. All prescriptions for the period of hospitalization were included in this study. Data collection occurred on all days of the week, including weekends. The following prescription solutions were excluded: 0.9% sodium chloride, 5% dextrose, blood products (except albumin), heparin for venous access and permeabilization, vaccines, phytomenadione, 1% silver nitrate eye drops (prescribed at birth for prophylaxis), parenteral nutrition, oxygen, and electrolytes (calcium gluconate, potassium chloride, magnesium sulfate and sodium bicarbonate) (Carvalho *et al.*, 2012).

Drugs were classified as level one (anatomical group) or three (pharmacological subgroup) according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO, 2014). They were also classified into two classes: (a) Unlicensed; this class included (i) unregistered drugs in Brazil or the U.S. that were chemically pure substances; (ii) drugs registered in Brazil or the U.S., but were modified to suit the pediatric needs of a newborn (such as crushing tablets to prepare a suspension or powder); and (iii) imported drugs (drugs imported from a country where they are licensed) (Neubert *et al.*, 2010; O'Donnell, Stone, Morle, 2002); and (b) Off-label; this class included drugs that were used outside of the recommended indication, dose, route of administration, and/or age described in the product registration for the ANVISA and FDA regulations. Off-label analysis for age took the corrected, postnatal age of the preterm group into account (Lass *et al.*, 2011; Neubert *et al.*, 2010; Carvalho *et al.*, 2003; Conroy, McIntyre, Choonara,

1999). All prescriptions were analyzed by two pharmacists to classify the drugs. In cases of disagreement, we requested review by a neonatologist.

The classification of drugs according to FDA criteria was conducted to compare our results with those of an international institution.

The off-label or unlicensed classifications, according to Brazilian regulations, were based on information contained on the drug label, which was accessed through consultation of the ANVISA site; this institution is responsible for the regulation of medicines in Brazil (Anvisa, 2014). For medicines whose package insert was not available on the site, package inserts of manufacturers of medicines in use at the investigated hospital during the study period were used. The classification of drugs according to the FDA was performed using Drugdex Micromedex™ (Drugdex, 2014). Micromedex™ provides registration data and directions approved by the FDA and this classification was used in research to evaluate the off-label use of prescription drugs (Smith *et al.*, 2012).

Statistical analysis

We calculated the sample size using the method for estimating the proportions of infinite populations because it would not be possible to estimate the number of newborns that would be admitted during the study period. To calculate the sample size, a rate of 90.0% exposure to drugs was used considering previously published studies about drug use in neonatology units (Jacqz-Aigrain, 2011; Neubert *et al.*, 2010; Conroy, McIntyre, Choonara, 1999). To estimate the extent of exposure to drugs of interest, a cohort of 138 newborns was considered to be sufficient, ensuring a margin of error equal to or less than 5% to the 5% level of significance.

A descriptive analysis was performed by determining the frequencies and percentages of categorical variables, and measuring the central tendency (mean and median) and dispersion (standard deviation and interquartile range) for quantitative variables. To compare categorical and quantitative variables, the Mann–Whitney test was used. Chi-square and Fisher exact tests were used to compare categorical variables. We used a significance level of 5%. All statistical analyses were performed using R software, version 2.15.1.

RESULTS

Descriptive parameters of newborns

The final recruited cohort included 157 neonates, including 89 (56.7%) males and 68 (43.3%) females. Regarding gestational age, 88 (56.0%) were preterm (Table I). The most frequent admission diagnoses were

TABLE I - Perinatal, demographic, clinical, and pharmacotherapeutic characteristics of the 157 neonates

Characteristics		Values
Gestational age in weeks	[median (interquartile range)]	36 (33–38)
24–27 [n (%)]	4 (2.5)	
28–30	[n (%)]	14 (8.9)
31–33	[n (%)]	28 (17.8)
34–36	[n (%)]	46 (29.3)
>37	[n (%)]	65 (41.4)
Gender	[male (%)]	89 (56.7)
Birth weight	[median (interquartile range)]	2350 (1805–2915)
≥2500 g	[n (%)]	66 (42.0)
2499–1500 g	[n (%)]	68 (43.3)
1499–1000 g	[n (%)]	17 (10.8)
<1000 g	[n (%)]	6 (3.8)
Pharmacotherapy		
Number of prescriptions		1187
Number of medicines		127
Number of drugs by newborn [mean (standard deviation)]		7.6 (7.9)
Prescriptions off-label according ANVISA n (%)		665 (56.0)
Prescriptions off-label according FDA n (%)		592 (49.9)
Prescriptions unlicensed according ANVISA n (%)		86 (7.2)

disorders related to gestation length and fetal growth. A total of 53 cases (33.8%) presented congenital malformations, 40 (25.5%) had respiratory conditions, and 33 (21.0%) had cardiovascular diseases during the perinatal period.

Drug prescriptions

The total number of prescriptions written was 1187, which encompassed 127 medicines. The mean number of drugs prescribed per newborn was 7.6. According to the ATC level 1 classification, drugs for the nervous system (group N) and systemic anti-infectives (group J) were the most frequently prescribed drugs, followed by agents that act on the alimentary tract and metabolism (group A), which comprised 356 (30.0%), 292 (24.6%), and 157 (13.2%) of prescriptions, respectively. Regarding ATC level 5, the most prescribed drug of all prescription items was fentanyl (9.3%), followed by multivitamin (8.4%) and gentamicin (7.9%).

Off-label prescriptions according to ANVISA

Off-label prescriptions accounted for 665 (56.0%) of the total according to the ANVISA criteria (Table I). Among the 157 neonates recruited, 150 (95.5%) received at least one off-label drug. The frequency of off-label drug use was 100.0% for extreme premature and very preterm newborns. In the other gestational age groups, the proportion of off-label use ranged from 93.8% to 96.4%.

As shown in Table II, drugs for the nervous system (group N), systemic anti-infectives (group J), and drugs targeting the alimentary tract and metabolism (group A) were the most frequent off-label prescriptions. Fentanyl and multivitamins were the most common off-label prescriptions in all strata of gestational age. The frequency of off-label use of midazolam, gentamicin, dipyrone, dopamine, and aminophylline was notable.

Among the 665 ANVISA off-label drugs, the most frequent off-label prescription category was the dose (99.5%), followed by indication (39.1%), route of administration (37.9%), and age (35.3%). Notably, the same drug can be the subject of more than one off-label category use.

Off-label prescriptions according to the FDA

According to FDA regulations, 592 (49.9 %) of all prescriptions recorded during the study period were off-label (Table I). Many newborns (113, 72.0%) received at least one drug off-label. The frequency of off-label drug use for extremely premature and very preterm babies was 100.0% and 92.9%, respectively. In the other gestational age groups, the proportion of FDA off-label prescriptions ranged between 63.0% and 73.8%. As shown in Table III, drugs for the nervous system (group N), systemic anti-infectives (group J), and cardiovascular system-targeting drugs (group C) were the most frequently used off-label from the prescriptions. Fentanyl and midazolam were the most frequently prescribed off-label drugs in all strata of gestational age according to FDA regulations. The frequencies of off-label use of gentamicin, ampicillin, cefazolin, cefadroxil, dobutamine, and dopamine were also notable.

TABLE II - ATC group of drugs used off-label according to ANVISA with a rate of use ≥4% among newborns, stratified by gestational age in weeks

Gestational age 24–27 weeks			Gestational age 28–30 weeks			Gestational age 31–33 weeks			Gestational age 34–36 weeks			Gestational age ≥37 weeks		
ATC Group	N	%	ATC Group	N	%	ATC Group	N	%	ATC Group	N	%	ATC Group	N	%
N	10	30.3	N	32	30.8	A	32	37.6	N	55	34.0	J	71	38.2
J	10	30.3	J	32	30.8	N	27	31.7	A	43	26.5	N	66	35.5
C	07	21.2	A	24	23.1	J	15	17.6	J	40	24.7	A	20	10.7
A	05	15.2	R	7	6.7	R	6	7.1	C	13	8.0	C	19	10.2
D	01	3.0	D	6	5.7	D	2	2.4	D	06	3.7	D	7	3.8
Total	33	100.0	C	3	2.9	B	1	1.2	M	05	3.1	B	3	1.6
			Total	104	100.0	C	1	1.2	Total	162	100.0	Total	186	100.0
						M	1	1.2						
						Total	85	100.0						

Similar to ANVISA, the most frequent off-label prescription category according to FDA regulations was dose (99.3%). Regarding indication, route of administration, and age, the proportions of off-label prescription use was 57.6%, 53.7%, and 57.3%, respectively.

Unlicensed medicines according to ANVISA and the FDA

The number of unlicensed drug prescriptions was 86 (7.2%) by ANVISA and 84 (7.1%) by FDA criteria (Table I). Anhydrous caffeine was the most frequently used unlicensed drug according to ANVISA across all ranges of gestational age. Other frequently used unlicensed medicines are shown in Table IV. A total of 30.6% and 12.7% of newborns received at least one unlicensed drug according to the ANVISA and FDA criteria, respectively.

Comparison between off-label ANVISA and FDA

The proportion of off-label drugs (56.0%) according to the ANVISA regulations was significantly greater than those according to the FDA regulations (49.9%; P-value = 0.002). Furthermore, the proportion of newborns who used off-label drugs (95.5%) by ANVISA criteria was significantly greater than that under the FDA criteria (72.0%; P-value < 0.001).

A comparison between the use of off-label drugs in the different age groups revealed no significant difference for either off-label ANVISA (P-value = 0.85) or off-label FDA (P-value = 0.15) uses.

For drug groups at ATC Level 1: drugs targeting the nervous system, anti-infectives for systemic use, and musculoskeletal system drugs showed a similar frequency of off-label uses between the FDA and ANVISA criteria.

DISCUSSION

This study reveals a high prevalence of off-label and unlicensed drug use, according to criteria of both ANVISA and the FDA. Additionally, an inverse relationship between this usage and gestational age of the newborns admitted to the neonatal unit was identified. The high frequency of off-label drug use, particularly among neonates who were 34 weeks or less by gestational age, is consistent with previously published national and international studies (Lass *et al.*, 2011; Neubert *et al.*, 2010; Dell'Aera *et al.*, 2007; Carvalho *et al.*, 2012; O'Donnell, Stone, Morley, 2002; Avenel *et al.*, 2000; Conroy, McIntyre, Choonara, 1999; Turner *et al.*, 1999). However, it is important to highlight the difficulty in comparing these present results with those of previous studies because of differences in the definitions used for off-label and unlicensed drugs in various studies.

Several definitions have been found in the literature for the term off-label and some may even be considered interchangeable with the definition of unlicensed drug. Some researchers include unlicensed drug within the definition of off-label drug (Kimland *et al.,* 2012; Mason, Pirmohamed, Nunn, 2012; Nguyen, Claris, Kassai, 2011; Dessi *et al.*, 2010). For this study, we chose to recognize differences between the two categories and advocate for the use of the two terms. We believe this provides

TABLE III - ATC group of drugs used off-label according to the FDA with a rate of use ≥ 4% among newborns, stratified by gestational age in weeks

Gestational age 24–27 weeks			Gestational age 28–30 weeks			Gestational age 31–33 weeks			Gestational age 34–36 weeks			Gestational age ≥37 weeks		
Group ATC	N	%	Group ATC	N	%	Group ATC	N	%	Group ATC	N	%	Group ATC	N	%
N	12	38.7	J	30	36.1	N	26	46.4	N	57	48.7	J	75	48.1
J	09	29.0	N	29	34.9	J	15	26.7	J	27	23.1	N	49	31.4
C	09	29.0	C	12	14.5	A	03	5.4	C	19	16.2	C	19	12.2
A	01	3.3	R	7	8.5	R	05	8.9	D	06	5.1	M	07	4.5
Total	31	100.0	A	4	4.8	M	02	3.6	M	05	4.3	D	03	1.9
			B	1	1.2	D	02	3.6	A	03	2.6	B	03	1.9
			Total		100.0	S	02	3.6	Total	117	100.0	Total	156	100.0
						B	01	1.8						
						Total	56	100.0						

TABLE IV - Frequency of newborns administered unlicensed ANVISA medicines by gestational age in weeks

Medicine	Gestational age in weeks					Total number of newborns	
	24–27	28–30	31–33	34–36	≥37		
	Number of newborns by gestational age						
	4	14	28	46	65	157	
	n	N	n	n	N	Total	%
Acetylsalicylic acid tablet	-	-	-	1	-	1	0.6
Alprostadil injectable solution	-	-	-	2	1	3	1.9
Amiodarone oral solution	-	-	-	-	1	1	0.6
Caffeine, anhydrous oral solution	2	6	10	1	2	21	13.4
Captopril oral solution	-	1	-	2	-	3	1.9
Captopril tablet	-	-	-	1	-	1	0.6
Carvedilol oral solution	-	-	-	1	-	1	0.6
Carvedilol tablet	-	-	-	1	-	1	0.6
Chloral hydrate syrup	1	-	-	-	-	1	0.6
Clonidine tablet	-	-	-	-	1	1	0.6
Clopidogrel tablet	-	-	-	1	-	1	0.6
Codeine, phosphate tablet	-	-	-	-	1	1	0.6
Digoxin tablet	-	-	-	-	1	1	0.6
Folic acid tablet	-	-	-	-	1	1	0.6
Furosemide oral solution	1	1	-	-	2	4	2.5
Hydrochlorothiazide oral solution	1	1	-	3	-	5	3.2
Hydrochlorothiazide tablet	-	1	-	-	-	1	0,6
Indomethacin oral solution	1	1	1	-	-	3	1.9
Lorazepam oral solution	1	-	-	3	1	5	3.2
Methadone oral solution	-	2	1	3	1	7	4.5
Methadone oral tablet	-	-	-	2	-	2	1.3
Methimazole oral solution	-	1	-	-	-	1	0.6
Methylcellulose eye drops	-	-	-	1	-	1	0.6
Nifedipine oral solution	-	-		-	1	1	0.6
Phenylephrine ophthalmic solution	-	-	1	1	1	3	0.6
Phenytoin sodium tablet	-	-	-	1	-	1	0.6
Propylthiouracil tablet	-	1	-	-	-	1	0.6
Pyrimethamine powder for oral use	-	-	-	-	1	1	0.6
Pyrimethamine tablet	-	-	-	-	1	1	0.6
Sildenafil oral solution	-	-	-	1	-	1	0.6
Sildenafil tablet	-	-	-	1	-	1	1.3
Spironolactone tablet	-	-	-	1	-	1	0.6
Spironolactone oral solution	-	1	-	2	1	4	2.5
Sulfadiazine tablet	-	-	-	-	1	1	0.6
Sulfadiazine oral solution	-	-	-	-	1	1	0.6
Thyroxine tablet	-	1	-	-	-	1	0.6
Ursodeoxycholic acid tablet	-	-	-	1	-	1	0.6

a better scaling of the problem, especially for research conducted in hospitals and with an age group with specific pharmacotherapy requirements, such as neonates.

The significant difference detected between the proportion of newborns with off-label prescriptions by the ANVISA and FDA drug regulations reflects the criteria used for medicine licensing and the quality of information provided in drug labels registered by both regulatory agencies. The highest proportion of off-label use by ANVISA standards suggests that the FDA provides more pharmacotherapeutic information and adopts criteria for the registration of medicines and development of labeling that come with the particularities of neonatology. Notably, it will provide more information on specific dosages for the neonatal age group. By contrast, drug labeling authorized by ANVISA frequently includes general dose information for pediatrics without considering the different age groups of neonates. We verify that prescriptions with off-label use, according to FDA criteria, showed a percentage of off-label use for indication, route of administration, and age that was greater than that of off-label according to ANVISA. Therefore, it is necessary that ANVISA undertake a general review of drug labeling to provide clearer and more defined data regarding neonatal use.

The discrepancies of information about drug use in neonatology between ANVISA and FDA identified in this study allow us to speculate whether the high rate of off-label drug use in neonates reflects the lack of studies in this age group or whether it occurs because the results of a few published studies are not reflected in the drug label. It is likely that a combination of the two theories has merit (Allegaert, Tibboel, van den Anker, 2013; Jacqz-Aigrain *et al.*, 2013; Lass *et al.*, 2011; Tafuri *et al.*, 2009).

The percentage of newborns receiving at least one unlicensed drug following ANVISA criteria (30.6 %) reflects the lack of interest from the Brazilian pharmaceutical industry in the production of medicines for pediatric use. Drugs for which available evidence has shown a positive impact on neonatal care, such as indomethacin and alprostadil, are not marketed in Brazil in drug dosage forms that are suitable for neonates. The economic interests are evident with the recent withdrawal from the Brazilian market of oral liquid formulations for phenytoin and furosemide, motivated by the low number of units sold. The use of unlicensed medicines is an indicator of the need for oral formulations appropriate to the neonates and newborns in the pharmaceutical market in Brazil. Moreover, the association between medication errors and use of unlicensed medicines has been previously described in the literature (Lass *et al.*, 2011; Conroy, 2011).

Given this scenario, the implementation in Brazil of equivalent measures to those of international initiatives developed by the FDA (i.e., the Best Pharmaceuticals for Children Act), the World Health Organization (the Make Medicines Child Size and WHO Model List of Essential Medicines for Children) and the European Medicines Agency (European Union's Pediatric Regulation) has become necessary to increase the availability of safe, effective, and quality medicines for children (Davis, Connor, Wood, 2012; Hopu *et al.,* 2012). These actions must be placed in context with the National Policy for Children's Health and with actions that encompass the drug regulatory agencies, pharmaceutical industry, academia, and those institutions responsible for the selection of drugs for the Brazilian health system. In the selection process of drugs for the health system, the age-specific needs of the neonatal and other pediatric groups should be considered.

To improve our understanding of the off-label and unlicensed use of drugs, we performed an analysis of the pharmacotherapeutic characteristics of drugs included in these categories. Among drugs that act on the nervous system, the highlight was the off-label use of anesthetics and analgesics (ATC level 3). Smith *et al.* (2012) found that the off-label use of medications is a common occurrence in the United States in the care of children undergoing anesthesia and sedation (Smith *et al.*, 2012). The authors acknowledged the challenges of clinical research with drugs in children and associated ethical and legal issues, but stressed that in this clinical setting, off-label use is a more acceptable practice than deprivation of treatment for a neonate. They mention that off-label use should be based on clinical care guidelines available in the literature and stress the importance of the physician's knowledge of the drugs that they prescribe.

In our study, off-label use occurred in almost all therapeutic classes that we identified. In the group of drugs that act on the alimentary tract and metabolism (ATC group A), the frequency of off-label prescription reflected the protocol of the unit at study, which advocates for the use of multivitamins in oral solution during hospitalization. This medicine was dosed off-label for all prescriptions. In a study carried out in France, as in our present study, multivitamins and an iron salt were the ATC class A drugs that contributed most to the frequency of off-label drug use (Nguyen, Claris, Kassai, 2011).

A systematic review explored the off-label use of sildenafil in the treatment of pulmonary hypertension of newborns. This usage is controversial because of the lack of well-designed clinical studies that demonstrate its safety and effectiveness in neonates (Shah *et al.*, 2011). In 2014,

the FDA issued a warning about the risks of chronic use of this drug in pediatric newborns, but without showing guidelines regarding use in the neonatal age group (FDA, 2012). Despite this drug having been used in only one newborn during this present study, it reflects the need for its use in neonatal care.

Drugs that act on the cardiovascular system (ATC group C) showed a higher prevalence of off-label use by the FDA criteria than by the ANVISA criteria as a consequence of the lack of indication of dopamine and dobutamine in neonates. However, in clinical practice, these drugs are widely present in clinical guidelines for the management of shock in the newborn. Given this situation and lack of therapeutic alternatives, it is important to seek our adequate information to ensure rational prescribing in neonates (Carvalho *et al.*, 2012).

Hydrochlorothiazide, classified in this study as unlicensed by both the ANVISA and FDA criteria, is used in the treatment of bronchopulmonary dysplasia of the newborn, but lack of knowledge about its long-term effects and efficacy in the clinic explains the lack of inclusion of this statement in the drug registration and the unavailability of drug dosage forms suitable for newborns. This drug, because of the lack of well-designed and controlled studies in neonates, is on the list of therapeutic priorities of the National Institute of Child Health and Human Development (NICHD) for investigation (NIH, 2014). Furosemide and spironolactone, used off-label in this study, also require further investigation to establish their efficacy and safety in bronchopulmonary dysplasia (Segar*,* 2012).

The prescription of unlicensed or off-label drugs is not illegal and can be clinically justified when there is no alternative therapy. However, it is undoubtedly a procedure associated with risks because of the absence of randomized controlled studies that explore the risk/benefit ratios for a drug (Cuzzolin, Zaccaron, Fanos, 2013). The use of drugs in the neonatal population with insufficient data on pharmacokinetics, pharmacodynamics, and side effects can result in undesirable effects in the short- and/or long-term. Short-term effects can include sub-dosing, resulting in therapeutic failure, or over-dosing, which implies a high risk of toxicity. Studies have suggested an increased risk of adverse drug reactions because of off-label use and the need to monitor adverse events associated with such usage (Ballard *et al.*, 2013; Jonville-Bera, Bera, Autret-Leca, 2005).

The safe and appropriate medication use in the neonatal period is an important and complex challenge because of the lack of clear data that should guide decision-making. According to Jain *et al.* (2012), despite this significant lack of information, physicians are required to optimize drug therapy in neonates and follow-up those results. Many institutions are developing such protocols using advanced tools for quality improvement; however, this practice remains rare.

More important than classifying a drug as off-label is to determine whether its use is evidence-based. It is important to have evidence that a drug is safe and appropriate to the newborn's clinical condition. Ideally, the evidence should be high level, obtained through well-designed, randomized clinical trials, and include information about the minimum effective dose. Unfortunately, the conditions of pediatric clinical practice are quite different, with a lack of detailed information that ensures safe and effective pharmacotherapy (Bonati, Pandolfini, 2011). Indeed, this study demonstrated that in Brazil the use of medicines for neonates is a serious problem for professionals in the pediatric field.

Updating the labeling of medicines of pediatric interest through evidence-based information represents an important strategy to reduce rates of off-label use and improve rational prescribing (Bonati, Pandolfini, 2011).

The results of this present study should be evaluated in the context of its limitations. In particular, the generalizability of our results is restricted because the study was completed in a NCU of a single tertiary care hospital. Thus, our results may not be applicable to those of less complex institutions. Another limitation is the sample size. It is important to emphasize that the prospective design of the study (covering prescription drugs administered during hospitalization), the classification of off-label (employing criteria of two regulatory agencies), and use of criteria of off-label and unlicensed (based on current literature concepts) are strengths of this study.

The frequency of off-label use of drugs in the neonatal unit investigated in this study was high. Nearly all newborns were exposed to at least one off-label prescription according to ANVISA regulations and 72.0% according to FDA regulations. In cases of extreme preterm neonates, exposure occurred in 100.0% of newborns according to both ANVISA and FDA criteria.

Data available about medicines registered in the FDA compared with the data available on medicines authorized by ANVISA is more complete with respect to indications, route of administration, and use according to gestational age.

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