Jornal de Pediatria
ISSN: 0021-7557
assessoria@jped.com.br
Sociedade Brasileira de Pediatria
Brasil

Carvalho, Clarissa G.; Ribeiro, Mariana R.; Bonilha, Mariana M.; Fernandes Jr., Mauro; Procianoy, Renato S.; Silveira, Rita C.

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Jornal de Pediatria, vol. 88, núm. 6, noviembre-diciembre, 2012, pp. 465-470
Sociedade Brasileira de Pediatria
Porto Alegre, Brasil

0021-7557/12/88-06/465
Jornal de Pediatria

Use of off-label and unlicensed drugs in the neonatal intensive care unit and its association with severity scores

Clarissa G. Carvalho,[1] Mariana R. Ribeiro,[2] Mariana M. Bonilha,[2] Mauro Fernandes Jr.,[2] Renato S. Procianoy,[3] Rita C. Silveira[4]

Abstract

Objective: To analyze the frequency of unlicensed (UL) and off-label (OL) prescriptions in neonates admitted to the neonatal intensive care unit of a tertiary care hospital and to determine their association with patients' severity.

Methods: Observational cohort study including drugs prescribed during hospitalization of neonates over a 6-week period between July and August 2011. The drugs were classified as UL and OL for dose, frequency, presentation, age group, or indication, according to an electronic list of drugs approved by the Food and Drug Administration. Patients were followed until hospital discharge or 31 days of hospitalization, with daily records of the Neonatal Therapeutic Intervention Scoring System (NTISS).

Results: We identified 318 prescription items for 61 patients (average of five items/patient); there were only 13 patients with appropriate use of medications (21%). A prevalence of 7.5% was identified for UL prescriptions and 27.7% for OL, and the most prevalent OL use was that related to age group - 19.5%. Fifty-seven medications were computed – one patient received 10 UL/OL drugs during hospitalization. The prevalence of OL uses was higher in preterm infants < 35 weeks and in those with higher severity scores (p = 0.00).

Conclusions: The prevalence of neonates exposed to UL/OL drugs during hospitalization was high, especially for those with higher NTISS scores. Although there is general appreciation that neonates, especially preterm infants, have a high rate of drug use, an assessment including different cultures and countries is still needed to prioritize areas for future research in the pharmacotherapy of this vulnerable population.

J Pediatr (Rio J). 2012;88(6):465-70: Drugs, drug labeling, injury severity score, neonatology.

Introduction

The Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMEA) in Europe are the authorities responsible for regulating drug registration.[1,2] In Brazil, one of the competencies of the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) is authorizing the registration of drugs within the national territory, based on data and information from internationally recognized regulatory agencies, but there is no specific regulation for drug registration and use in children yet.[3]

In some countries there are reports showing high prevalence of use of non-approved or off-label (OL) drugs,

1. MSc, Pediatrics, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. Neonatologist, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.
2. Medical student, UFRGS, Porto Alegre, RS, Brazil.
3. Full professor, Pediatrics, Faculdade de Medicina, UFRGS, Porto Alegre, RS, Brazil. Head, Serviço de Neonatologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.
4. Professor, Pediatrics, Faculdade de Medicina, UFRGS, Porto Alegre, RS, Brazil. Head, Unidade de Follow-up de Prematuros, Serviço de Neonatologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

No conflicts of interest declared concerning the publication of this article.

Financial support: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) - research iniciation grant.

Suggested citation: Carvalho CG, Ribeiro MR, Bonilha MM, Fernandes Jr M, Procianoy RS, Silveira RC. Use of off-label and unlicensed drugs in the neonatal intensive care unit and its association with severity scores. J Pediatr (Rio J). 2012;88(6):465-70.

Manuscript submitted May 25 2012, accepted for publication Jul 25 2012.

http://dx.doi.org/10.2223/JPED.2231

either at medical offices, admission and surgical units or at pediatric and neonatal intensive care units (NICUs), mostly due to prescribers' ignorance of these peculiarities.[4-8] OL drugs are defined as those prescribed in a different manner to label recommendations in terms of age group, dose, frequency, presentation, administration route, or indication for use in children. Therefore, OL use refers to the non-approved use of a drug for a purpose other than that approved by the FDA.[4]

Critically ill newborns may receive from 15 to 20 intravenous drugs per day, most of them unlicensed (UL) and OL.[9] Conceivably, severity could be considered to justify the prescription and use of non-approved or OL drugs in NICUs, calling the risk/benefit ratio in defense; hence the importance of evaluating this condition.

Due to the scarce literature describing the prevalence of prescription of drugs inappropriate for neonates, as well determining the relationship between higher use of OL drugs and newborn's severity, the aim of the present study was to analyze the frequency of UL and OL prescriptions in neonates admitted to the NICU of a tertiary care hospital and to determine their association with patients' severity during NICU stay.

Methods

This was a prospective cohort study including all newborns admitted to the NICU of the institution over a 6-week period between July and August 2011. During this period, prescriptions, physiologic factors, and use of technology were assessed for the calculation of severity scores. The analysis did not include the following: prescriptions of blood and its by-products, Total Parenteral Nutrition (TPN), oxygen and other gases, vitamin K, silver nitrate, routine care of umbilical stump, and vaccines. No patient or pathology was considered as an exclusion criterion.

The newborns were followed for a period of up to 31 days, and the analysis included only data corresponding to the hospitalization period. This period was chosen because, in a Brazilian study on the application of the Neonatal Therapeutic Intervention Scoring System (NTISS) as a tool for comparing healthcare practices in NICUs, it was shown that there was a gradual and progressive decreasing pattern up to the 31st day of hospitalization.[10] The NTISS is an index that measures the amount of technology used and results from the combination of eight healthcare parameters: respiratory, monitoring, cardiovascular, drug therapy, metabolic/nutrition, procedural, transfusion, and vascular access. A significant association was observed between NTISS and estimates of clinical outcome, of risk of death, and of prediction of high healthcare costs with newborns in the NICU.[11]

Besides the application of the NTISS, each prescribed drug was evaluated regarding the approval of use to determine if it was an UL or an OL use. Prescriptions were classified by the main author and study advisors (all neonatologists), according to the FDA list of approved drugs, into: UL for products manufactured at the hospital, not approved in general, or imported, and OL for administration route, dose, presentation, frequency, indication, and age group appropriateness.

The newborns were followed by the healthcare staff of the NICU. For each patient admitted to the NICU during the study period, a form with demographic data and gestational and perinatal history was generated. The severity score NTISS was calculated and recorded on a daily basis by the main author. The prescription was also revised on a daily basis by the team responsible for data collection, which comprised three medical interns and a senior supervisor. Indication, administration route, dose, presentation, frequency, and age group appropriateness were recorded. No intervention was performed in the patients – the research team was not identified by the health care staff, in order to avoid changes in prescription patterns or medical records.

The project was approved by the Research Ethics Committee of the hospital; in addition, the authors signed an undertaking for data use and parents gave a free and informed consent.

Statistical analysis

Sample size calculation was based on a previous study to detect a difference of 18% in the percentage of OL or UL drug use between a more vulnerable group, illustrated in this study by preterm newborns, and a possibly less severe group, represented by full-term babies (86% of use for preterm infants and 68% for term infants)[12]; considering an α value = 0.05 and a power of 80%, a total of 96 patients would be needed.

Data were stored and analyzed with the Statistical Package for Social Sciences software, version 18.0. The chi-square test was used to calculate the association between groups. The severity scores were analyzed and compared with the frequency of OL or UL prescriptions using the generalized linear model, due to the asymmetry of NTISS. The level of statistical significance for all analyses was set at $\alpha = 0.05$. The evolution of total NTISS during infants' hospitalization was followed using median values for the variable, with good graphical visualization.

Results

A total of 129 newborns were consecutively admitted, and 318 prescription items were recorded. Of those, 68 used only oxygen therapy and glucose solution, with no other

valid prescription items; for the other newborns, five items of prescription/patient were recorded, on average, during hospitalization. Among all prescription items, a total of 57 drugs were identified.

The prevalence of "appropriately" prescribed medications, according to the FDA list of approved drugs, was 64.8%, with a prevalence of 7.5% for UL drugs and of 27.7% for OL drugs. The most prevalent OL use was related to age group – 19.5%.

Forty-eight patients received some kind of OL or UL drug, corresponding to 78.7% of the newborns whose prescription included only valid items. A child ended up receiving 10 OL or UL drugs during hospitalization.

Average length of stay was 10 days, and there were four deaths. The most frequent reason for admission was neonatal jaundice (35%), followed by early respiratory dysfunction (16%), prematurity (13%), sepsis (12.5%), malformation (8.5%), and hypoglycemia. Only two patients had a history of maternal fever; 59% of the patients were male and 41% were female; there was no difference between the groups. The most prescribed drugs, on the whole, are described in Table 1.

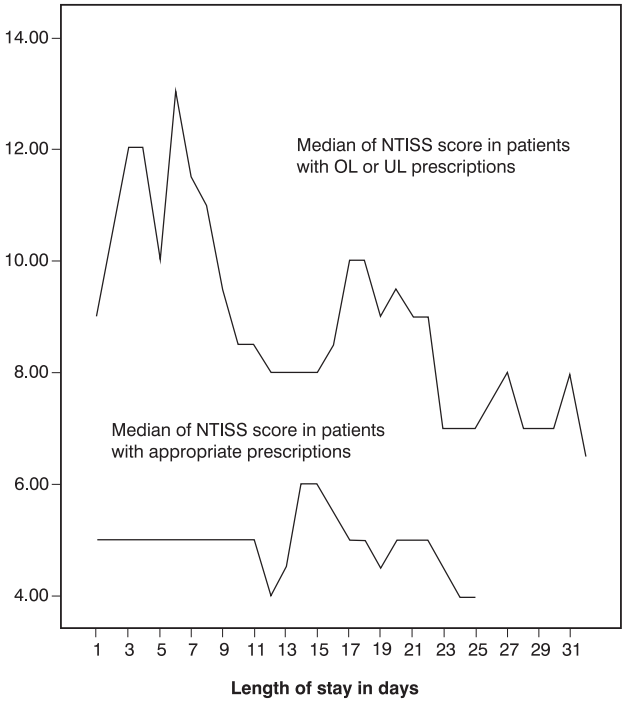
Table 1 - List of the 10 most frequently prescribed drugs in the intensive care unit during the study period

Drug	Number of prescriptions	%
Ampicillin	26	8.2
Gentamicin	25	7.9
Vancomycin	14	4.4
Multivitamins	14	4.4
Morphine	14	4.4
Fentanyl	14	4.4
Paracetamol	12	3.8
Glycerin	11	3.5
Phenobarbital	11	3.5
Amikacin	11	3.5

UL drugs included dipyrone, chloral hydrate, and caffeine. The only OL drug for dose was ampicillin, as shown in Table 2. As to frequency, patients were found to use ampicillin, cefotaxime, and dexamethasone at intervals different from those recommended in the FDA list. OL drugs for age group were glycerin, paracetamol, diazepam, dopamine, ibuprofen, zidovudine, filgrastin, ranitidine, domperidone, cefalexin, interferon, milrinone, noradrenaline, omeprazole, sildenafil, magnesium sulfate, insulin, albumin, and mannitol. As to OL use for indication, metoclopramide, cefepime, vancomycin, and hydrocortisone should be mentioned.

The prevalence of preterm infants < 32 weeks was higher in the OL/UL group compared with the group with appropriate prescriptions (14.6 vs. 0%), as well as the prevalence of preterm infants between 32 and 35 weeks (23 vs. 10%, p < 0.001). The prevalence of babies with birth weight < 2,500 g was 42% in the OL/UL group vs. 21% in the appropriate group (p = 0.004). Table 3 shows the distribution of prescriptions and sample characteristics according to gestational age.

Overall, NTISS score showed higher medians in patients using OL or UL drugs, as shown in Figure 1. From the 25th day of hospitalization on, all patients presented some kind of OL or UL prescription, not allowing for analyses on median differences. The comparison of median evolution during hospitalization showed higher values for the OL or UL group, which was observed using a generalized linear model analysis (Figure 1).



NTISS = Neonatal Therapeutic Intervention Scoring System; OL = off-label; UL = unlicensed.
p = 0.001. Generalized linear model analysis.

Figure 1 - Daily median values of the Neonatal Therapeutic Intervention Scoring System – comparison between patients with appropriate prescriptions and those with off-label or unlicensed prescriptions

Discussion

In our study, we demonstrated that the use of OL drugs is frequent in neonatology, considering that 78.7% of patients with valid prescription items received some kind

Table 2 - More frequently prescribed drugs/class in the study sample

Class of drugs	Prevalence % - n	More frequent drugs
Approved	(64.8% - 206)	Gentamicin, multivitamins, morphine, fentanyl
Unlicensed	(7.5% - 24)	Caffeine, dipyrone, and chloral hydrate
OL for dose	(4.1% - 13)	Ampicillin
OL for frequency	(1.9% - 6)	Ampicillin, cefotaxime, and dexamethasone
OL for age group	(19.5% - 62)	Paracetamol, glycerin, dopamine, zidovudine
OL for indication	(2.2% - 7)	Hydrocortisone, vancomycin, metoclopramide, and cefepime

OL = off-label.

Table 3 - Distribution of prescriptions and sample characteristics according to gestational age

Variables	< 32 weeks	32-35 weeks	35-37 weeks	> 37 weeks	Total
Number of patients – n (%)	7 (5.4)	19 (14.6)	26 (20)	77 (60)	129 (100)
Birth weight (m)	1,200 g	2,267 g	2,503 g	3,266 g	2,853 g
Standard deviation	441 g	568 g	401g	584 g	785 g
Length of stay (m)	22.5	17.9	9	7.3	10
Standard deviation	11.4	8	7.5	7	8.8
% patients using OL drugs (n)	100% (7)	57.9% (11)	19.2% (5)	32.5% (25)	62% (48)
Number of prescriptions	50	46	38	184	318
% OL prescriptions (n)	38% (19)	39% (18)	26% (10)	35.3% (65)	35.2% (112)
NTISS 24 h med	22 (13-27)	8 (5-13)	7 (4-9.2)	5 (4-7)	6 (4-9)

NTISS 24 h med = median of the Neonatal Therapeutic Intervention Scoring System in the first 24 hours after admission for each gestational age group; OL = off-label.

of OL or UL drug. OL drugs for age group corresponded to the majority of these prescriptions, representing nearly half of patients with drug prescriptions – 52.5%. We also observed a higher prevalence of OL uses among preterm infants below 32 weeks – all of them used some kind of OL drug. Additionally, the prevalence of patients with weight below 2,500 g was twice as high in the group using OL or UL drugs compared with that observed in the group using appropriate drugs.

Our prevalence is slightly lower than that from European studies which described a prevalence between 80 and 93% in four NICUs.[13-16] A possible explanation refers to the fact that our sample was more heterogeneous, with few premature infants with very low weight and extreme immaturity (only 5.4%), which is exactly the group of neonates that has been described as the most exposed to OL drugs in Europe.

It is important for every country to know its situation regarding drug use, because there are legal differences in the authorization status of medical products and clinical practice among countries.[2,3,17] A study conducted in England,[13] over a period of 13 weeks, including 70 newborns (70% preterm) obtained a prevalence of 54.7% for OL and 10% for UL prescriptions. On the other hand, a French study[18] with 40 newborns (88% premature infants with extremely low weight) found prevalences of 63% for OL and 10% for UL prescriptions. In Spain,[19] an analysis of 48 neonates (60% preterm) showed that 50% of the prescriptions were OL and 13% UL. These findings demonstrate the variability among countries.

Low weight preterm infants and ill term infants are the most exposed to OL or UL drugs. The number of administered drugs is inversely proportional to gestational age and/or newborn's weight.[20] Physiological immaturity affects drug absorption and distribution, due to the composition of body compartment and to water content, protein binding, hemodynamic factors, and drug metabolism (renal or hepatic clearance).[21] Exposure to multiple agents

is also a factor for an increase in the incidence of adverse events in neonates: many drugs can be incompatible or interact with one another.[22]

In the group of OL drugs for age group, we found medications with a well established use in protocols, clinical trials, and meta-analyses, but with no controlled studies meeting the strict FDA criteria – which includes both drugs for severe conditions, such as pulmonary hypertension (sildenafil, magnesium sulfate, milrinone), hyperglycemia in the extremely premature infant (insulin), shock (albumin, noradrenaline, dopamine), patent ductus arteriosus (ibuprofen), and frequently used drugs, such as those for gastroesophageal reflux disease (domperidone, ranitidine, omeprazol), paracetamol for pain relief, glycerin, suppository for difficult evacuation, as well as prophylaxis for vertical HIV transmission in exposed neonates.

An interesting finding of our study is the classification of ampicillin as OL for dose, because the service routinely gives 300 mg/kg/day of ampicillin for covering *Streptococcus agalactiae* in central nervous system, even when there is no evidence of meningitis. Other groups also classified this medication as OL.[19,23]

Dopamine was equally classified as an OL drug, due to the lack of data on its long-term safety in exposed infants, which is in agreement with other published studies.[16,23] This is a very important fact, considering its widespread use in treatment protocols for shock in the newborn – and the absence of other agents that are equally effective and show an acceptable safety profile.

Dipyrone is not traditionally a FDA-approved drug, due to the risk of inducing aplastic anemia e agranulocytosis. The other drugs that we classified as UL were chloral hydrate and caffeine, which refer to compounding drugs from the hospital pharmacy, because there is no commercial presentation available for this age group, similar to a Dutch study that obtained a high prevalence of UL prescriptions (62%) due to amount of drugs manufactured at that hospital.[24] Caffeine citrate, known for treating apnea in prematurity, is also mentioned in other studies.[16,24,25]

Chloral hydrate is frequently used as a sedative in procedures such as nuclear magnetic resonance imaging tests, during which the infant must remain still. Although it is widely used, recent studies show a decrease in hemoglobin saturation after the procedure in preterm newborns and babies with mores comorbidities,[26] which makes its use highly arguable – despite the few available pharmacological alternatives for the same purpose.

Among all active substances licensed by the EMEA from October 1995 to September 2005, only 33% were licensed for use in children, 23% in infants, and only 9% in neonates, this being the reason why neonatology is an area that frequently uses OL drugs.[27] The medical practice requiring the use of OL drugs is acceptable in order to provide the most appropriate treatment for the patient,[17] since science and medicine evolve faster than FDA bureaucratic procedures.

The barriers for conducting appropriate research in the development of medicine for children are a long-standing issue. The cost of studies with children is high compared with the size of the potential market, which implies a poor financial return for pharmaceutical companies; besides that, there are difficulties in study design, as well as a small number of eligible patients and lack of adequate controls with the same age, the time spent to complete studies in children compared with adults, long time to obtain approval, unique and complex ethical aspects with regard to research with children, considerations on risk/benefit for those who are not able to consent for themselves yet – all these aspects make newborns "therapeutic orphans."[2]

A positive feature of our study, and also new, is the establishment of the association between the use of OL or UL prescriptions and severity scores. On the whole, the NTISS score showed higher medians in patients using OL or UL drugs during hospitalization compared with patients with appropriate medication use or with no prescription for a valid drug. The association between patients' severity and use of OL or UL drugs ethically justifies the use of these "inappropriate" drugs.

However, a limitation of the study was the inclusion of patients with no pharmacological therapeutics and using items such as oxygen, phototherapy or glucose solution, which characterizes the treatment of early respiratory dysfunction, jaundice, and hypoglycemia, highly frequent in neonatal admission. Due to the prevalence of these diseases, it was not possible to exclude these patients from the analysis, which could possibly overestimate the association between NTISS and OL prescriptions. On the other hand, this makes feasible the validation of these results in less complex intensive care units, allowing for the generalization of our data.

In view of the presented aspects, it is possible to state that the prevalence of newborns exposed to OL or UL drugs during hospitalization is high, especially in those with higher NTISS scores. Although there is general appreciation that neonates, especially preterm infants, have a high rate of drug use, an assessment including different cultures and countries is still needed to prioritize areas for future research in the pharmacotherapy of this vulnerable population.

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Correspondence:
Clarissa G. Carvalho
Av. Mostardeiro,157, cj 1206
CEP 90430-001 - Porto Alegre, RS - Brazil
Tel.: +55 (51) 9714.4468
E-mail: clarissagc@yahoo.com.br