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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Off-label and unlicensed drug treatments in Neonatal Intensive Care Units: an Italian multicentre study

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Abstract
Purpose The use of medicines among newborns admitted to intensive care units is characterized by a high prevalence of *off-label*/unlicensed use and a wide variability in the absence of international guidelines. A prospective cross-sectional study was organized with the aim to analyse drug prescriptions among all 107 Italian level III neonatal intensive care units.
Methods An online questionnaire was used to collect detailed information for each newborn, and a classification was made about the license status of all prescriptions. In addition, prescriptions were analysed taking into account a practical guide prepared by the Italian Society of Neonatology (ISN).
Results The 1-day survey (May–July 2014) regarded 220 newborn infants admitted to 36/107 Italian neonatal intensive care units: 191 prematures and 29 born at term. In total, 720 prescriptions (corresponding to 79 different drugs) were analysed: 191 (26.5 %) followed the terms of the product license, 529 (73.5 %) were *off-label* or unlicensed: 193/220 newborns (87.7 %) received at least one off-label/unlicensed prescription. Antiinfectives were the most common medicine used, followed by respiratory drugs and antianaemics; in an off-label manner, the most common was cardiovascular and central nervous system (CNS) drugs, gastrointestinals and antiinfectives. The most common categories of off-label use were age (34.4 %) and dosing frequency (20.6 %). Compared to ISN practical guide, prescriptions adhered more frequently to indications (100 % for ampicillin/sulbactam, >80 % for ampicillin, fluconazole, fentanyl, ranitidine and vancomicin).
Conclusions Our results confirm the high prevalence of off-label/unlicensed drug use in the neonatal population and underline a better adherence to indications based on clinical practice, suggesting the need to update information contained in the data sheets of medicines.

Keywords Newborn · Medicines · *Off-label* use · Variability

Introduction

Variability in drug use among neonatal population is a widespread phenomenon [1], and different factors such as the absence of drug research and the particular characteristics of the newborn patient could contribute. Among these factors, the use of medicines without a marketing authorization (unlicensed) or outside the terms of product license (*off-label*) plays an important role and is common in neonatal intensive care units (NICUs) due to a lack of systematic specific clinical testing and limited prescribing information [2]. This use is neither illegal nor incorrect, being often supported by a longstanding clinical experience but may expose the newborns to further risks as demonstrated by the higher incidence of adverse drug reactions (ADRs) [3] and prescription errors [4] observed in NICUs.

In this study, drug prescriptions have been analysed in a sample of newborns admitted to a representative sample of Italian NICUs, with the purpose to determine the extent and nature of off-label (OL) and unlicensed (UL) drug use in this setting. Moreover, the prescription behaviour was compared with indications contained in a practical guide to the use of drugs in newborns [5] prepared by the Neonatal

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Pharmacotherapy Study Group (NPSG) of the Italian Society of Neonatology (ISN).

Methods

All 107 level III Italian NICUs were contacted via email at the beginning of 2014 with a letter of invitation and requested to participate to a prospective cross-sectional cohort study. On the basis of an online questionnaire (Google form), demographic and drug data for each newborn admitted to the NICU were recorded by a structured staff neonatologist in a day chosen within each ward between May and July 2014 (1-day survey) after sought and information to local ethics committees. As personal identifying data of the infants could neither directly or indirectly be attributed to a specific individual and the study design did not affect the health care of the included patients, a formal written consent for participation in this study was not obtained.

Data collected from each newborn present in NICU in the day chosen (with the exception of neonates who did not receive any drug treatment) included date of birth, sex, gestational age and weight, Apgar score, diagnosis and all information about each drug administered during the day chosen: formulation, dose and frequency, route of administration, length of therapy, indication for use and tolerability. Parenteral nutrition solutions, nutritional supplements such as vitamins and probiotics and standard intravenous fluids were recorded but not considered and analysed for the purposes of this study.

For each drug, a licensed or unlicensed use was determined according to the *Italian Drug Compendium 2013*. This classification was based on information derived from product data sheets (package insert, Summary of Product Characteristics).

Drug prescriptions were classified into four groups: (1) drugs following the marketing authorization; (2) off-label drugs with no information for paediatric use; (3) drugs licensed for paediatric use, but off-label for age, dose, frequency, route of administration, length of therapy and clinical indication; (4) unlicensed drugs, including any change in the pharmaceutical form made by the hospital pharmacy (personalized galenic preparations) or by authorized manufacturers (special formulations) to make the drug suitable for use in neonatal care and drugs imported from a foreign country.

In addition, every prescription was compared with a practical guide proposed by the NPSG, containing information about all medicines commonly used in NICU and available both as book [5] and online to all Italian neonatologists.

Data were collected in a database and summarized using standard descriptive methods. Categorical variables related to prescription behaviour and geographical location were compared by χ^2 analysis: Statistical significance was defined as $p \leq 0.05$.

Results

Thirty-six NICUs (34 % of all Italian level III NICUs, comprising hospital and academic wards), 17 in Northern Italy, 13 in Centre Italy and 6 in Southern Italy, participated in the survey accessing the online questionnaire: each ward recorded a median number of six charts (range 2–22). NICUs participating in this study should be considered representative of the regional distribution and of the number of beds/ward (in every case>4, with a maximum of 36 beds in some cases).

A total of 220 newborn infants were treated with at least one drug in the day chosen. As specified in Table 1, 191

Table 1 Baseline characteristics of the newborns

Parameter	Patients
	(*n*=220)
Male gender	131 (59.5 %)
Gestational age (weeks)	
≤27	82 (37.3 %)
28–31	62 (28.2 %)
32–36	47 (21.4 %)
≥37	29 (13.2 %)
Birth weight (g)	
≤1000	93 (42.3 %)
1001–1499	47 (21.4 %)
1500–2500	49 (22.3 %)
>2500	31 (14.0 %)
Small for gestational age	28 (12.7 %)
Apgar score first min	
≤3	44 (20 %)
4–6	80 (36 %)
7–10	96 (44 %)
Apgar score fifth min	
≤3	10 (4.6 %)
4–6	30 (13.6 %)
7–10	180 (81.8 %)
Diseases	
Anaemia	39
Cardiovascular problems	37
Gastrointestinal problems	44
Respiratory problems	158
Sepsis	33
Suspected/proven infections	157
Other	44
Endotracheal intubation at birth	8
Mechanical ventilation	10
O_2 supplementation	4
Phototherapy	12
Catheterization	70
Surgical intervention	18

newborns (86.8 %) were preterm (born before the 37th week of gestation, according to the International Conference on Harmonization) and 29 (13.2 %) were born at term. The most of neonates (140/220, 63.6 %) resulted to be very low birth weight (VLBW) or extremely low birth weight (ELBW) infants, and 28/220 (12.7 %, 7 VLBW and 21 ELBW) were small for gestational age (SGA). On the day chosen for data collection, the median postnatal age was 3.32 weeks, being 189/220 newborns in the first month of life.

In total, 720 prescriptions corresponding to 79 different medicines were written. Each newborn received a median number of four different drugs (range 1–9). In addition, other 163 treatments (comprising parenteral nutrition solutions, multivitamins, probiotics and electrolytic solutions) were applied to newborns. The most common route of administration of drugs was intravenous (78.7 %), followed by oral (14 %) and subcutaneous (4.3 %): Intravenous administration was used more frequently in NICUs of Centre Italy (82.8 vs 78 and 69.6 %, $\chi^2=7.044$, $p=0.031$). Other routes (topical, inhalatorial, intramuscular, endotracheal) were used rarely.

The drugs prescribed, classified in groups according to the Anatomical Therapeutic Chemical Classification system, are reported in Table 2. Antiinfectives were the most commonly used medicines (316 prescriptions), followed by respiratory drugs (152 prescriptions) and antianaemics (73 prescriptions).

Newborns (193/220, 87.7 %) received at least an off-label or unlicensed prescription.

Among the 720 prescriptions, 191 (26.5 %) followed the terms of the marketing authorization, while 529 (73.5 %) were off-label (425/720, 59 %) or unlicensed (104/720, 14.5 %). The most common categories of off-label use were age (248/720, 34.4 %) and dosing frequency (148/720, 20.6 %). Cardiovascular drug prescriptions resulted 100 % off-label in the absence of neonatal indications, while antiinfectives and Central Nervous System (CNS) drugs were used off-label in more than 75 % of cases. Based on geographical area, wide inter-NICU significant differences have been observed as regards off-label or unlicensed prescriptions: Off-label prescriptions resulted lower in Southern Italy (46.7 vs 59.9 % in Northern Italy and 62.3 % in Centre Italy, $\chi^2=6.941$, $p=0.031$), while unlicensed prescriptions were higher in Northern Italy (20.6 vs 7 and 8.7 %, respectively, in Centre and Southern Italy, $\chi^2=26.296$, $p=0.000$).

The most frequently administered drugs resulted caffeine, fluconazole, ampicillin, ampicillin/sulbactam, gentamicin, netilmicin, amikacin, vancomicin, fentanyl, epoetine, folinic acid and ranitidine: globally, prescriptions derived from these medicines accounted for 66.8 % of all prescriptions (481/720), among which 346 resulted off-label or unlicensed (72 %).

Prescriptions (100 %) of folinic acid resulted unlicensed in the absence of an adequate formulation (galenic preparation), while in 52 % of cases, caffeine continued to be administered as galenic preparation in the presence of a licensed product, particularly in Northern Italy (77.7 vs 27 and 15 %, $\chi^2=36.963$, $p=0.000$).

The other drugs, prescribed in an off-label manner, are reported and analysed in Table 3 as regards deviation from license status and no adherence to ISN practical guide.

Prescriptions (100 %) of fluconazole, fentanyl and ranitidine resulted off-label in the absence of specific indications for preterm neonates. As regards ampicillin, amikacin and netilmicin, off-label prescriptions were >80 % and mainly regarded differences in dose or frequency of administration. Instead, off-label prescriptions resulted lower for gentamicin (64 %), ampicillin/sulbactam (43 %), vancomycin and epoetin (29 %).

Compared to ISN practical guide, prescriptions adhered more frequently to the suggested indications (only about one fourth of prescriptions deviated by indications) and differences regarded dose or frequency of administration. The adherence was total for ampicillin/sulbactam and >80 % for ampicillin, fluconazole, fentanyl, folinic acid, ranitidine and vancomicin.

Table 2 Drug prescriptions in NICUs

	Total prescriptions ($n=720$)	UL prescriptions ($n=104$)	OL prescriptions ($n=425$)	Reason
Antiinfectives	316	–	239 (75.6 %)	OL for age ($n=76$), frequency ($n=139$), dose ($n=20$), formulation ($n=4$)
Respiratory drugs	152	62 (40.8 %)	26 (17.1 %)	OL for age ($n=25$) or indication ($n=1$)
Antianaemic drugs	73	30 (41.1 %)	23 (31.5 %)	OL for age ($n=15$) or frequency ($n=8$)
CNS drugs	62	–	47 (75.8 %)	OL for age ($n=42$), frequency ($n=1$), formulation ($n=4$)
Cardiovascular drugs	56	–	56 (100 %)	OL for age
Gastrointestinal drugs	46	12 (26.1 %)	29 (63 %)	OL for age
Analgesics/ antipyretics	10	–	2 (20 %)	OL for age
Hormones	5	–	3 (60 %)	OL for age

OL off-label, *UL* unlicensed

Table 3 Drugs most frequently administered in an off-label manner

	Total prescriptions (n=337)	OL prescriptions (n=260)	Reason	No adherence to ISN protocol (n=111)	Deviation
Ampicillin	61	56 (92 %)	OL for frequency	2 (3 %)	Frequency
Fluconazole	51	51 (100 %)	OL for age, dose or frequency	6 (12 %)	Frequency
Gentamicin	42	27 (64 %)	OL for frequency or formulation	16 (38 %)	Dose or frequency
Fentanyl	33	33 (100 %)	OL for age	1 (3 %)	Frequency
Ampicillin/sulbactam	28	12 (43 %)	OL for dose or frequency	–	–
Epoetine	28	8 (29 %)	OL for frequency	9 (32 %)	Frequency
Netilmicin	26	22 (85 %)	OL for frequency or formulation	9 (35 %)	Dose or frequency
Amikacin	25	23 (92 %)	OL for dose or frequency	17 (68 %)	Dose or frequency
Ranitidine	22	22 (100 %)	OL for age	2 (9 %)	Dose or frequency
Vancomicin	21	6 (29 %)	OL for dose or frequency	2 (10 %)	Dose or frequency

OL off-label

Discussion

This survey, the first nationwide study of this kind comprising about one third of all Italian level III NICUs, confirms the large variability in drug use among newborns admitted to NICUs and high off-label/unlicensed drug prescriptions. Moreover, the higher adherence to the indications contained in the ISN practical guide suggests that a standardization of practice regarding drug use could lead to a reduction in the variability observed.

Off-label/unlicensed drugs are often used in neonatal care, and in many situations, this is the only therapeutic alternative due to the lack of availability of suitable licensed/labelled drugs. In the last years, some encouraging initiatives have been taken with the aim to reduce the use of off-label/unlicensed drugs in the paediatric population. Anyhow an increase in registered clinical trials and drugs approved has been observed [6, 7]. However, despite the introduction of the European Paediatric Regulation in 2007, little has changed as regards neonatal population, with only one quarter of Paediatric Investigation Plans (PIPs) addressing newborns [8] and very few labelling changes specific for the neonatal population [9]. Therefore, most of the exposure to medicines remains off-label for neonates, as underlined in a recent review [10].

Our data are in line with previously published data, regarding European [11–25] and Italian NICUs [26–28]: More than 80 % of newborns received at least one off-label or unlicensed medicine and only about one fourth of prescriptions followed the terms of the marketing authorization, with a 59 % prevalence for off-label drug use and a 14.5 % prevalence for unlicensed drugs. On the basis of the geographical distribution, these mean data reflect wide inter-NICU differences, not only due to newborn characteristics (gestational age, diseases) but also to local policies (i.e. use of galenic preparations). As regards differences in off-label uses, a possible explanation could be the higher presence in some NICUs of ELBW infants, subjects particularly at risk that require multiple treatments, while the higher unlicensed prescriptions observed in Northern Italy are mainly related to the use of a galenic preparation of caffeine, cheaper compared to the available licensed formulation.

If we analyse prescriptions related to the most frequently administered drugs, some considerations about the use of antibiotics in the neonatal population are needed, being this therapeutic class the most administered for prevention and therapy of infections. Information contained in data sheets rarely reflect clinical practice, as demonstrated by a higher adherence to the ISN practical guide particularly as regards dose and frequency of administration. In detail, ampicillin prescriptions deviated by the suggested ISN recommendations in only 3 % of cases and ampicillin/sulbactam completely adhered, compared respectively to 92 and 43 % off-label prescriptions. This derives by a clear discrepancy between generic indications contained in data sheets (100 mg/kg/daily divided in three doses for ampicillin and 75–150 mg/kg/daily divided in two doses for ampicillin/sulbactam) and how these antibiotics are effectively given to newborns taking into account the characteristics of the patient and the indication (prophylactic or therapeutic use and severity of the infection): 50–100 mg/kg every 8–12 h depending on gestational age and postnatal age (ampicillin), 50–75 mg/kg every 12 h or 50–100 mg/kg every 6–8–12 h depending on severity of the infection (ampicillin/sulbactam). Similar differences as regards dose and frequency of administration also emerge with some aminoglycosides (gentamicin, netilmicin and amikacin) and vancomycin: In clinical practice, dosage schemes of these antibiotics are different among NICUs and regard often longer intervals of administration and sometimes higher doses. These aspects were underlined also by other authors who compared antibiotic prescriptions related to 110 newborns admitted to NICUs of some hospitals in the UK, Italy and Greece: the number of off-label prescriptions (in total 218/290, 75 %) resulted significantly higher in Italy and Greece (92 % compared to 63 % in the

UK) and mostly regarded gentamicin and amikacin given at different total daily doses or frequency [29].

Fluconazole, fentanyl and ranitidine, widely used in NICUs as also demonstrated by our data, are given outside the registered age.

Fluconazole, approved by EMA for use in term newborns, is emerging as the drug of choice for antifungal prophylaxis even if its routine use in VLBW and ELBW infants is controversial as regards its real efficacy in reducing risk of death or invasive candidiasis [30–32]. Despite these controversies and the lack of license status, the scientific societies are currently supporting antifungal prophylaxis with fluconazole at a dose of 3–6 mg/kg twice weekly for all neonates <1000 g and/or ≤27 weeks of gestation admitted in NICUs where frequency of invasive fungal infections is relatively high [33]. In a cross-sectional survey (part of the FP7 TINN project), 51 % of European NICUs adhering to the project reported to apply an antifungal prophylaxis with fluconazole [34]. Our data underline the common use of this drug in preterm newborns (100 % of prescriptions off-label for age regarding 78 % of NICUs) and the variability in the dosage scheme. In fact, compared to the indications contained in the data sheet, fluconazole was administered following different dosage schemes only partially justified by neonatal characteristics and indications: 3–6–12 mg/kg every 24–48–72 h, mostly given intravenously for 14–35 days. This variability, reported also by other authors in Italy [35] and in other European countries [34], resulted significantly lower taking into account the ISN protocol (only 3 % prescriptions deviated).

Fentanyl is among the analgesics most frequently prescribed in NICUs to provide procedural pain relief and its use increased in the last 10-year period due to a better understanding of the harmful effects of severe pain and a higher expertise to manage analgesics in neonates: the completion of a PIP for fentanyl was scheduled in June 2015 [25], but at this moment, no information is available. From our analysis of data, fentanyl was used in 33 % of NICUs while morphine or remifentanil were preferred in other wards.

In Italy, ranitidine is used for gastroesophageal reflux disease in newborns despite that its efficacy and safety have not been established in the neonatal population [36, 37]: recently, some authors demonstrated an association between ranitidine use and risk of infections and necrotizing enterocolitis in neonates [38]. From our data, ranitidine continues to be used in NICUs while the only drug approved for the neonatal population, domperidone, was administered only to five neonates. A possible explanation could be that, on the light of no robust evidence of domperidone efficacy and safety [39], the drug present on the market for a longer time has been preferred.

Among antianaemic drugs, the most commonly used were epoetine, in 29 % of cases off-label for frequency (24–72 instead of 48 h), and folinic acid available as galenic preparation: in preterm newborns, the efficacy of folinic acid in preventing anaemia has been reported [40], but there is no consensus on treatment duration, dose or formulation to be used.

Finally, some considerations are needed about caffeine, commonly administered for the treatment of apnea of prematurity, that continues to be used as galenic preparation in 16/36 NICUs (44.4 %), particularly in Northern Italy, despite the availability of a product licensed (Peyona®): In the absence of RCTs comparing the safety profiles of the extemporaneous caffeine and the product licensed, the lower costs of galenic preparation could explain this prescription behaviour.

This survey has undoubtedly some limitations, such as the self-report nature of the study but overall the number of neonates and NICUs included, that do not allow a more accurate analysis of the data and require a further in-depth study that will be organized in the next months. However, given the paucity of data available as regards the neonatal population, our recording and analysis of drug prescriptions given to newborns admitted to a sample of Italian NICUs (representative of the other units not included) could be a first step to introduce a data collection system useful to evaluate the efficacy and safety of drugs used in this vulnerable patient population in an attempt to harmonize prescription behaviour and to minimize drug-related risks. Moreover, the observed better adherence to indications based on clinical practice (NPSG practical guide) suggests the need to update information contained in the data sheets of medicines.

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Contributions of author statement Rocco Agostino and Laura Cuzzolin defined the study and the online questionnaire. Laura Cuzzolin performed the analysis of the data and wrote the first draft of the manuscript. Rocco Agostino critically reviewed the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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