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SHORT COMMUNICATION

# Unlicensed and off-label drug use: a prospective study in French NICU

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Off-label and unlicensed drug use to treat children is widespread in various countries (1). Because of insufficient clinical trials in paediatric population, health professionals are forced to extrapolate the results of studies carried out on adults. A systematic review including thirty international studies on off-label/unlicensed (OLUL) neonatal prescription shows the rates of such usage ranging from 55 to 80% (2). In France, data of such prescription in neonates are lacking. For that reason, we aimed to update information on the extent of OLUL prescriptions in neonates.

This prospective, observational study was conducted at two neonatal intensive care units (NICU) in Lyon, France. All drugs administered to neonates during 2012 were recorded, and their labelling status was assessed. Patients were eligible if they received at least one medicine during their stay. The data including gestational age (GA); birthweight (BW); gender; date of birth; hospital stay; and administered medication data with generic names, dosage, indication, route of administration, frequency and duration of treatment were extracted from patients' electronic file (Philips, IntelliSpace Critical Care an Anesthesia version F.00.001). Patients were followed up until hospital discharge. For each child, if two or more courses of the same drug were prescribed in the same manner, they were only reported once. Blood products, oxygen therapy, enteral and parenteral nutrition, and standard intravenous replacement solutions were excluded.

The primary reference source for determining licensed labelling was the summary of product characteristics (SPCs) in a French independent formulary named Theriaque 2013. Licensed drugs included medicines used within the prescribed terms of the marketing authorisation. We considered as unlicensed (i) the modified use of licensed drugs (such as crushing tablets to prepare a suspension), (ii) drugs that are licensed in a certain form, but manufactured in another formulation under a special license (such as the liquid preparation of a drug that is licensed only in tablet form), (iii) the use of chemicals as drugs when no pharmaceutical grade preparation is available, (iv) drugs used before a license has been granted, (v) imported drugs (drugs imported from a country where they are licensed) and (vi) drugs without any product license or without any information for paediatric use in the SPCs.

Off-label use was defined as the use of a drug outside the scope of a drug's approved label, that is at different doses or frequencies, in different indications, in different age groups, administrated by an alternative route, or in a formulation not approved in children. Off-label analysis for age took the corrected, postnatal age in the preterm group into account. Physicians were aware of the study's goal. The local research ethics committee approved the study protocol.

All data were analysed using R software 2.15.2 (http://cran.r-project.org/). Descriptive and analytic statistics were performed. To identify determinants of OL or UL prescrip-

**Abbreviations**
ATC, anatomical therapeutic chemical; BW, birthweight; EMA, European Medicines Agency; GA, gestational age; GER, gastro-esophageal reflux; NICU, neonatal intensive care unit; OL, off-label; SPCs, summary of products characteristics; UL, unlicensed; US, United States.

tions, nonadjusted and adjusted logistic regression models were built. For categorical variables, trends were tested.

A total of 910 patients were included during the study period. A total of 236 (26%) were full term and 671 (73.7%) were preterm neonates. Median GA was 34 weeks (range 31–37 weeks), and median BW was 2040 g (ranged 1530–2270 g). Of 8891 total prescriptions, median prescription number per child was 8 (range 5–13), 35.2% (CI 95%: 35.2–36.2) of the prescriptions were licensed, 5.2% were unlicensed, and 59.5% were in an off-label manner. A total of 94.8% of neonates received at least one ULOL drug. The drug exposure rates per 100 admissions were inversely correlated with GA. A total of 58.8% (CI 95%: 57.8–59.8) of the OL prescription was age related (Table 1). The vitamin (B) and antibiotic (J) were two classes most commonly used in our newborns, and about 76.6% (CI 95%: 74.8–78.4) and 44.8% (CI 95%: 42.5–47.1) of their prescriptions were off-label for age.

Tables 2 and 3 show the detail of the most frequently prescribed drugs in NICU and their labelling status.

In multivariate analysis, given gender, length of the stay and centre, preterm between 28 to 31 weeks GA appeared to be more than 10-fold higher risk to expose to OL/UL drugs compared to preterm after 32–36 weeks GA,

**Table 1** Demographic and general prescriptions characteristics

| Demographics | <28 weeks gestational age (GA) | 28–31 weeks 6 days GA | 32–36 weeks 6 days GA | ≥ 37 weeks gestational age | Total |
|---|---|---|---|---|---|
| Number of children admitted (%) | 59 (6.5) | 188 (20.7) | 424 (46.7) | 236 (26) | 910 |
| Gender M/F | 40/19 | 102/85 | 238/186 | 140/96 | 522/387 |
| Median gestational age (weeks) Interquartile range (IQR) | 27 (25–27) | 30 (29–31) | 34 (33–35) | 39 (38–40) | 34 (31–37) |
| Median birthweight (gram) (IQR) | 810 (720–985) | 1360 (1140–1620) | 2060 (1777–2402) | 3295 (2885–3625) | 2040 (1530–2270) |
| Median no. of hospitalization days (IQR) | 78 (45.5–101.5) | 41 (20–60) | 18 (9–31) | 8 (5–15) | 18 (8–38.75) |
| Prescription characteristics | | | | | |
| Number of prescriptions | 1274 | 2454 | 3377 | 1756 | 8891 |
| Number of products used | 86 | 92 | 94 | 100 | 142 |
| Number of prescription per child. Median (IQR) | 21 (13–30.5) | 11.5 (9–17) | 7 (5–10) | 6 (4–11) | 8 (5–13) |
| Number of off-label prescriptions (%) | 741 (58.2) | 1547 (63) | 2335 (69.1) | 648 (36.9) | 5287 (59.5) |
| Number of unlicensed prescriptions (%) | 103 (8) | 148 (6) | 109 (3.2) | 103 (5.9) | 466 (5.2) |
| Number of UL or OL prescription (%) | 865 (67.9) | 1713 (69.8) | 2486 (73.6) | 798 (45.4) | 5753 (64.7) |
| Number of children with off-label or unlicensed prescription (%) | 59 (100) | 188 (100) | 418 (98.6) | 195 (82.6) | 863 (94.8) |

**Table 2** The most commonly prescribed drugs and their labelling status (% of all prescriptions and 95% confidence interval)

| Drug name | Prescriptions Total N, 8891 | Per cent (95% CI) | Labelling status |
|---|---|---|---|
| Phytomenadione | 1137 | 12.8 (12.1–13.5) | Off-label for age if < 37 GA |
| Vitamin AEDC* | 875 | 9.8 (9.2–10.4) | Licensed |
| Calcium folinate | 497 | 5.6 (5.1–6.1) | Off-label for age/route of administration |
| Amikacin sulphate | 479 | 5.4 (4.9–5.9) | Off-label for age |
| Ferrous fumarate | 440 | 4.9 (4.5–5.3) | Off-label for age |
| Rifamycin sodium | 411 | 4.6 (4.2–5) | Off-label for age if < 37 GA |
| Paracetamol | 378 | 4.3 (3.9–4.7) | Off-label for age if< 37 GA, and intravenous route† |
| Caffeine citrate | 346 | 3.9 (3.5–4.3) | Licensed |
| Cefotaxime sodium | 292 | 3.3 (2.9–3.7) | Licensed |
| Amoxicillin sodium | 258 | 2.9 (2.6–3.2) | Licensed |
| Midazolam hydrochloride | 241 | 2.7 (2.4–3) | Licensed/Off-label in certain condition‡ |
| Sodium chloride 10% | 211 | 2.4 (2.1–2.7) | Off-label for route of administration |
| Vancomycin hydrochloride | 211 | 2.4 (2.1–2.7) | Licensed |

*Uvesterol ADEC (retinol 3000 IU, ergocalciferol 1000 IU, Alpha-tocopherol 5 mg, ascorbic acid 50 mg/mL).
†In Theriaque, lLicensed if > 37 GA in oral/intravenous administration.
‡In Theriaque, licensed if < 32 GA, no bolus, continuous intravenous, dose 0.03 mg/kg/h OR > 32 GA, no bolus, continuous intravenous, dose 0.06 mg/kg/h. If one of them is not respected, midazolam was classified as off-label for age, dosage or route of administration.

**Table 3** The most commonly off-label and unlicensed drugs (% of all prescriptions)

| Off-label drugs (%) | Unlicensed drugs (%) |
|---|---|
| Calcium folinate (5.6) | Glucose monohydrate 10% (1.3)*† |
| Amikacin sulphate (5.4) | Norepinephrine (0.6)† |
| Ferrous fumarate (4.9) | Ketamine hydrochloride (0.5)† |
| Rifamycin sodium (3.9) | Glucose phosphate disodique (0.5)* |
| Sodium chloride 10% (2.4) | Pentobarbital (0.4)† |

*Use of chemicals as drugs when no pharmaceutical grade preparation is available.
†Drugs without any information for paediatric use in the SPCs.

respectively (OR = 0.106, 95% CI 0.045–0.254, $p < 0.0003$ versus OR = 0.011, 95% CI 0.002–0.06, $p < 0.0003$). After adjusting for gender, gestational age and centre, each additional day of stay multiplies the risk of OL/UL prescription by 1.1, 95% CI (1.04–1.16), $p < 0.0003$.

In our study, of 8891 total prescriptions, 5.2% were unlicensed and 59.5% were off-label. The proportion of such prescriptions was similar to those reported previously in NICUs, in Italy (6 and 48%) (3), in Palestine (8 and 55%) (4), in Germany (6 and 58%) (5) and in Sweden (7 and 57%) (6). A total of 94.8% of infants in NICUs received at least one unlicensed or off-label drug. This rate was similar than those reported in NICUs by other centres worldwide (3–7). To our knowledge, this study is the first in neonates within a large cohort and with an important study period in France. Unlike other French studies, which used Vidal as a reference source, we used Theriaque 2013, one of the most independently and well-documented sources. The high rate of off-label use in neonates is not only due to the lack of trials but also due to the lack of information in the SPCs (8). To reduce such practices, the information in the SPCs should be updated and harmonised using all scientific, approved sources. We believe that a specific reference source for drugs used in neonates in France would be helpful, because they integrate drugs studied specifically in this group and not reported either in Theriaque or Vidal.

Off-label use of folinic acid and ferrous fumarate was common in the study wards. In preterm newborns, the efficacy of folinic acid and iron in preventing anaemia has been previously reported (9,10). However, there is no consensus on the treatment duration, the dose prescribed or the drug formulation to be used. More evidence is needed for these two drugs in preterm newborns. Phytomenadione use in the prevention of vitamin K deficiency bleeding in newborn is well-established (11). In our units phytomenadione is given orally at the dosage of 2 mg once a day for three days or by one intravenous route dose of 1 mg on the first day to all neonates. This drug is then continued with 2 mg once a week regardless of gestational age and weight for neonates feeding on breast milk. Although there is a consensus on the fact that all premature infants should receive phytomenadione, neonatologists use a variety of doses, routes of administrations and formulations (12). To date, few studies have been carried out to refine vitamin K dosage, efficacy or duration of treatment or to assess vitamin K status after prophylaxis. Contrary to studies carried out internationally (13) in which gentamicin sulphate is common, in our study, we observed the frequent use of amikacin sulphate. Theriaque provides information on the use of this drug in infants, but not in newborns or preterm neonates. Data on the pharmacokinetics, efficacy and tolerability of these antibiotics in newborns and preterm infants have been reported by several studies (14). More comprehensive information for amikacin sulphate in preterm infants should be available in reference source, and further research is needed to clarify the benefice–risk between gentamicin sulphate and amikacin sulphate in neonates. Midazolam hydrochloride and fentanyl hydrochloride were commonly used in an off-label manner for neonates in our study. The efficacy and safety of such drugs have not yet been sufficiently studied. In 2009, our first study in neonatal ward revealed 3% of domperidone use in OL for age and indication to treat gastroesophageal reflux (GER) (7). In 2012, we observed that this drug was no longer prescribed in two centres, but an increase use of esomeprazole in OL for age and for indication (1.5% of all prescription vs 0.3%) was notified. Proton pump inhibitors are often prescribed off-label to treat symptoms associated with GER in neonates, although there is a lack of extensive safety and efficacy data. A recent study by Davidson et al. (15) has shown that esomeprazole did not reduce signs or symptoms of GER vs placebo in term and preterm neonates. Extemporaneous preparations were also common, and underline the lack of a suitable commercial paediatric formulation, as illustrated by the orally use of morphine hydrochloride trihydrate in withdrawal syndrome. It was observed that norepinephrine was commonly used in critical situation but to our knowledge, neither pharmacokinetic/pharmacodynamics model nor efficacy and safety study of norepinephrine have been established strong as evidence for preterm population.

Only two centres participated in our study making the generalisability of our results difficult. However, our sample size was large and the study period was lengthy (12 months).

Our study showed that the OLUL prescriptions in NICU were common. This might expose neonates to high risk of medication errors and adverse drug reactions, and rise ethical dilemma between not prescribing treatments with potential therapeutic benefit and jeopardising children's safety. Their legal, financial and ethical implications call for urgent action: to develop neonatal clinical trials and harmonise available sources on neonatal drug utilisation.

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## CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

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