

# Variability in drug use among newborns admitted to NICUs: a proposal for a European multicentre study

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*“We cannot always make our patients better,  
but we can always make them worse”*  
Bill Silverman

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The use of drugs in newborns admitted to Neonatal Intensive Care Units (NICUs) is characterized by a great variability in the management of the most common diseases and is a widespread phenomenon observed both within and between different countries.

An interesting paper published some months ago [1] reported data on a preliminary part of the Treat Infections in Neonates (TINN) project set up under the 7<sup>th</sup> Framework Programme [2], describing the use of ciprofloxacin and fluconazole in 189 NICUs of 25 different European countries. These two drugs, respectively used to treat sepsis caused by multiple resistant organisms [3] and invasive candidiasis [4], are included in the EMA's priority list of off-patent products with the highest need for studies in newborns [5] since there is insufficient data on their pharmacokinetics, efficacy and safety in neonates [6, 7]. From this paper emerged a heterogeneous situation as regards the treatment of bacterial and fungal neonatal sepsis within and between European countries. In detail, ciprofloxacin was used in 25% of NICUs in absence of guidelines about the use of ciprofloxacin for neonatal sepsis and mainly on the basis of a standard written protocol. This antibiotic was administered in dosages that varied enormously (ranging from < 10 mg/kg/day to > 30 mg/kg/day), with the most commonly used regimen being 20 mg/kg/day. As regards fluconazole, considered by the IDSA guidelines a possible option for treatment of invasive candidiasis, 70% of NICUs administered this antifungine on the basis of a standard written protocol. The dosages used varied significantly (3-6-12-20 mg/kg) and only 16% of NICUs administered the recommended dose of 12 mg/kg/day reported by IDSA guidelines. Moreover, the interval between administrations also varied, following a 24-h (41% of NICUs), 48-h (24% of NICUs) or 72-h (19% of NICUs) interval. From the analysis of questionnaires emerged concerns expressed by respondents about antibiotic resistance and lack of safety data in neonates.

This aspect of variability in drug use does not regard only the treatment of neonatal infections, but also other medicines commonly used in the neonate in the first period of life.

In fact, the same scenario emerged as regards the treatment of PDA in preterm newborns. A questionnaire was sent to 24 European Societies of Neonatology and Perinatology and the analysis of data received from 45 NICUs of 19 European countries revealed a wide variation among countries as regards the use of NSAIDs to treat PDA, partly

explained by the definition/diagnosis criteria of PDA. Intravenous indomethacin (mostly a 30-60 min infusion) was used in 32 NICUs (71%), intravenous ibuprofen in 16 NICUs (36%) and oral ibuprofen, preferred for its low cost, in 13 NICUs (29%). 45% of NICUs applied two courses of treatment and 27% prescribed a third one (usually not indicated). Prolonged treatments were mentioned by 45% of wards, despite the greater incidence of enterocolitis and changes in renal function. Almost all NICUs treated hemodynamically significant PDA, while prophylactic treatments were applied in 2 NICUs [8]. To treat remains an unresolved issue, due to a lack of data that could clearly give a universal recommendation. In presence of a hemodynamically significant PDA, a consensus of the Iberian Society of Neonatology recommends to start the treatment between day 2 and 5 of life to increase the probability of success [9].

Undoubtedly, given the unique characteristics of the neonatal population, it could be justified in some situations to apply a treatment on individual basis. However, other factors could contribute to this variability in drug use. First of all, it is common the absence of evidence-based guidelines defining the better treatment for the most common diseases diagnosed in the newborn such as PDA and sepsis. Moreover, it is widespread the use of drugs in an *off-label* manner, given the difficulty to perform clinical studies in the neonatal population. Some years ago, a review by Cuzzolin et al. [10] underlined the high number of newborns (> 80%) receiving an *off-label* treatment. Despite an improvement in rational prescribing for pediatric population, including more than 500 labelling changes [11], *off-label* drug use remains an important health issue for neonates, as confirmed more recently by other authors [12-16]. This kind of use of medications makes the neonatal population highly vulnerable to adverse drug reactions (ADRs) [17] and medication errors [18]. In fact, the potential ADRs rate calculated in pediatric wards is 3 times higher compared to the other patient populations and even more significantly higher in NICUs, with most of ADRs involving uncorrected doses or unapproved formulations [17, 19, 20]. In a review published by Chedoe et al. [21], eleven studies were identified on the frequency of medication errors in NICUs: rates varied widely between studies (the highest rate was 5.5 medication errors per 100 prescriptions) and the majority of studies identified dose errors as the most common type of error.

Differences in clinical practices between NICUs need to be addressed at a European level.

Therefore, a multicentre study involving different NICUs of European countries could be useful to harmonize drug use in the neonate. The collection and recording of data regarding medicines given to newborns admitted to NICUs is an instrument of knowledge useful to evaluate the efficacy and safety of drugs used in this vulnerable patient population, with the purpose to give to all newborns identical health care opportunities [22].

### Declaration of interest

The Author declares that there is no conflict of interest.

### References

- Pandolfini C, Kaguelidou F, Sequi M, Jacqz-Aigrain E, Choonara I, Turner MA, Manzoni P, Bonati M. Wide intra- and inter-country variability in drug use and dosage in very-low-birth-weight newborns with severe infections. *Eur J Clin Pharmacol*. 2013;69(4):1031-6.
- Jacqz-Aigrain E. Drug policy in Europe Research and funding in neonates: current challenges, future perspectives, new opportunities. *Early Hum Dev*. 2011;87(Suppl 1):S27-S30.
- Gendrel D, Chalumeau M, Moulin F, Raymond J. Fluoroquinolones in paediatrics: a risk for the patient or for the community? *Lancet Infect Dis*. 2003;3:537-46.
- Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:503-35.
- European Medicines Agency (EMA). Updated priority list (revised) for studies into off-patent paediatric medicinal products. Doc. Ref. EMA/197972/2007. London: EMA, 2007.
- Kaguelidou F, Turner MA, Choonara I, Jacqz-Aigrain E. Ciprofloxacin use in neonates: a systematic review of the literature. *Pediatr Infect Dis*. 2011;30:e29-37.
- Manzoni P, Mostert M, Jacqz-Aigrain E, Farina D. The use of fluconazole in neonatal intensive care units. *Arch Dis Child*. 2009;94:983-7.
- Guimarães H, Rocha G, Tomé T, Anatólitou F, Sarafidis K, Fanos V. Non-steroid anti-inflammatory drugs in the treatment of patent ductus arteriosus in European newborns. *J Matern Fetal Neonatal Med*. 2009;22(Suppl 3):77-80.
- Golombek SG, Sola A, Baquero H, Borbonet D, Cabañas F, Fajardo C, Goldsmit G, Lemus L, Miura E, Pellicer A, Perez JM, Rogido M, Zambosco G, Van Overmeire B. First SIBEN clinical consensus: diagnostic and therapeutic approach to patent ductus arteriosus in premature newborns. *An Pediatr (Barc)*. 2008;69(5):454-81.
- Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf*. 2006;5(5):703-18.
- American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. *Pediatrics*. 2014;133(3):563-7.
- Dessi A, Salemi C, Fanos V, Cuzzolin L. Drug treatments in a neonatal setting: focus on the off-label use in the first month of life. *Pharm World Sci*. 2010;32(2):120-4.
- Nguyen KA, Claris O, Kassai B. Unlicensed and off-label drug use in a neonatal unit in France. *Acta Paediatr*. 2011;100(4):615-7.
- Lass J, Kaar R, Jogi K, Varendi H, Metsvaht T, Lutsar I. Drug utilisation pattern and off-label use of medicines in Estonian neonatal units. *Eur J Clin Pharmacol*. 2011;67(12):1263-71.
- Oguz SS, Kanmaz HG, Dilmen U. Off-label and unlicensed drug use in neonatal intensive care units in Turkey: the old-inn study. *Int J Clin Pharm*. 2012;34(1):136-41.
- Laforgia N, Nuccio MM, Schettini F, Dell'Aera M, Gasbarro AR, Dell'Erba A, Solarino B. Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. *Pediatr Int*. 2014;56: 57-9.
- Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. *Eur J Clin Pharmacol*. 2012;68(1):21-8.
- Stavroudis TA, Shore AD, Morlock L, Hicks RW, Bundy D, Miller MR. NICU medication errors: identifying a risk profile for medication errors in the neonatal intensive care unit. *J Perinatol*. 2010;30(7):459-68.
- Fabiano V, Mameli C, Zuccotti GV. Adverse drug reactions in newborns, infants and toddlers: pediatric pharmacovigilance between present and future. *Expert Opin Drug Saf*. 2012;11(1): 95-105.
- Du W, Lehr VT, Lieh-Lai M, Koo W, Ward RM, Rieder MJ, Van den Anker JN, Reeves JH, Mathew M, Lulic-Botica M, Aranda JV. An algorithm to detect adverse drug reactions in the Neonatal intensive Care Unit: a new approach. *J Clin Pharmacol*. 2013;53(1):87-95.
- Chedoe I, Molendijk HA, Dittrich ST, Jansman FG, Harting JW, Brouwers JR, Taxis K. Incidence and nature of medication errors in neonatal intensive care with strategies to improve safety: a review of the current literature. *Drug Saf*. 2007;30(6):503-13.
- Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. *Fundam Clin Pharmacol*. 2003;17(1):125-31.