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EDITORIAL

Off-label and unlicensed drugs in neonatology

Medicamentos off-label y sin licencia en neonatología

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At present, a significant proportion of neonates admitted to neonatal intensive care units (NICUs) receive off-label or unlicensed drugs, mainly due to the scarcity of evidence on drug efficacy and safety in the neonatal period. In Spain, a recent study in a level IIIC NICU conducted by Sucasas-Alonso et al. found that 22.5% of prescriptions were off-label and 8% unlicensed, and that as many as 59.5% of the patients received at least one prescription under one of these conditions.[1]

Unlicensed refers to use of unauthorised drugs, drugs contraindicated in the neonatal period, imported drugs or formulations compounded in the pharmacy, the latter of which account for a large part of the variability of unlicensed drug prescription found between studies conducted in different countries. *Off-label* refers to the use of authorised drugs under conditions other than those detailed in the summary of product characteristics approved by the competent regulatory agent in terms of age, indication, dosage, interval between doses or the route of administration. The substantial variability in off-label prescription is due to the criterion used to define it; thus, Geißler et al. reported a proportion of off-label prescription of 39.2% in one NICU in 2014 considering exclusively the age criterion,[2] whereas a multicentre study conducted in Italy by Cuzzolin and Agostino found a proportion of off-label prescription of 59.5% over the total prescriptions taking into account criteria in addition to age, such as the indication, dose, dose schedule, route of administration and duration of treatment.[3] In a study published in the current issue of ANALES DE PEDIATRÍA, Lima-Costa et al. analysed off-label and unlabelled prescriptions in a NICU in Brazil based on the criteria established by 2 agencies: the National Health Surveillance Agency (ANVISA) of Brazil and the Food and Drug Administration (FDA) of the United States.[4] They found a higher frequency of unlicensed prescription with the application of the FDA criteria (24.6 vs 17.2%; $P < .01$). However, when it came to off-label prescription, the frequency was lower applying the criteria of the FDA (49.3 vs 52.6; $P < .01$), as this agency is more specific in regard to the ages and indications for which use is authorised. The agreement analysis found the greatest disparities in age and indication criteria, especially for drugs acting on the cardiovascular system and the central nervous system. This study contributes new evidence on the issue of unapproved drug prescription in neonatology.

Pharmacological treatment in neonates is affected by the immaturity of the hepatic clearance systems and renal function in this population, which differs from other age groups not only in pharmacokinetics, but also in pharmacodynamics. This is particularly relevant in the NICU setting due to the underlying conditions that affect critically ill neonates and the high proportion of patients born preterm or small for gestational age. Thus, more paediatric and neona-

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tal studies are required to achieve a reduction in off-label and unlicensed prescription. This was the main objective of the legislation introduced in the European Union in 2007: to reduce the use of off-label drugs in the paediatric age group and to increase the clinical evidence in this population to improve the safety of pharmacotherapy. Some of the measures adopted to this end were the extension of patents for paediatric drugs and the establishment of public funding programmes to facilitate research outside the pharmaceutical industry. However, as the study by Geißler et al. demonstrates, there were no changes in the patterns of off-label prescription between 2004 and 2014 associated with the legislation introduced in the European Union in 2007, of which a very clear example is the fact that despite changes in regulation, 100% of neonates born preterm before 28 weeks' gestation received at least 1 off-label or unlicensed drug.[2] The number of drugs licensed for use in newborns continues to be small, for while European law mandates that trials include this population in the authorization process for any new drugs, this obligation does not extend to drugs that are already marketed to which, consequently, the protection of the patent does not apply, providing little incentive for pharmaceutical companies to change the situation, as future profits would be relatively small relative to the costs of the research that would be required.

In the current issue of ANALES DE PEDIATRÍA, Piñeiro Pérez et al., on behalf of the Committee on Medicines of the Asociación Española de Pediatría (Spanish Association of Pediatrics, AEP), reflect on some of the theoretical, legal and practical aspects of unapproved prescription in paediatrics. We believe that the concise yet rigorous exposition by the authors, in the form of questions and answers, will contribute to a clearer understanding to the very important subject of drug prescription in paediatrics, particularly in neonatal care and neonatal intensive care units.[5]

The fact that some drugs go from being considered off-label to being authorised and vice versa evinces that authorization does not necessarily imply that more evidence is available on those drugs. This is particularly evident in older drugs, for which fewer requirements needed to be met for authorization compared to current requirements. In any case, it is obvious that off-label prescription is neither illegal nor inappropriate and is often a decision based on years of clinical experience and a lack of alternative drugs stemming from the low availability of adequate drugs currently licensed. Nevertheless, this carries an increased risk for neonates, as evinced by the higher frequency of adverse drug reactions and medication errors in this age group.

The number of off-label prescriptions becomes significantly smaller if the criteria used to define them includes, in addition to those of regulatory agencies, the criteria of other databases, such as the databases available in Spain in the field of paediatrics (*Pediamécum*, launched by the Committee on Medicines of the AEP in 2012) or for the general population (*Bot Plus*, created by the General Council of Boards of Pharmacy of Spain), which provide standardised and updated information on medicines. Similarly, Cuzzolin and Agostino showed that taking as reference the guidelines developed by the Neonatal Pharmacotherapy Study Group of the Italian Society of Neonatology, only one fourth of prescriptions deviated from the recommendations, compared to a proportion of off-label or unlicensed prescription of 73.5% based on the criteria of regulatory agencies.[3] This demonstrates that there is a marked discrepancy between the general indications included in the summary of product characteristics and the recommendations given taking into account patient characteristics and indications. In neonatal care, this is particularly frequent in antimicrobial prescription.

In our opinion, the solution of this problem requires the development of policies providing incentives for research in the neonatal age group. However, while we await further and improved evidence allowing a reduction in unapproved drug prescription, efforts should be made to achieve greater homogeneity in the information available on pharmacological agents used in the neonatal population.

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