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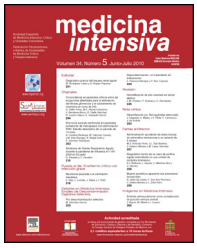

ORIGINAL

# Drug utilization pattern in children and *off-label* use of medicines in a pediatric intensive care unit☆

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**KEYWORDS**
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Children;
Neonates

**Abstract**
*Objective:* This study aims to assess the prescription profile and license status of drugs used in a neonatal and pediatric intensive care unit (NPICU).
*Methods:* A prospective observational study was conducted on a dynamic cohort of children admitted to an NPICU ($N = 81$) in a tertiary hospital (Granada, Spain). All prescriptions were classified as *off-label* or *unlicensed* based on the Summary of Product Characteristics (SPC).
*Results:* Of a total of 601 prescriptions, the patients received a mean of $7.4 \pm 6$ drugs each. The most commonly prescribed drugs corresponded to classes J (anti-infectious, systemic use) N (nervous system) and C (cardiovascular). A little over one-half of the prescriptions were *off-label* (52%), usually due to dosages differing from the SPC recommendations (79%), followed by different indications (13.5%), age (5%) and administration route (2.5%). In this NPICU, *unlicensed* usage represented only 5% of all prescriptions.
*Conclusions:* This study contributes data on prescription of this kind in a Spanish NPICU, revealing at least one *off-label* prescription in 89% of the children and at least one *unlicensed* use in 22.3%. These are high figures, but are to be expected given the inclusion of newborn infants and

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the critical care setting. Even though such usage follows clinical protocols, we underscore the dual need to base treatment on the best available evidence, and to upgrade the SPC accordingly.


**PALABRAS CLAVE**
Cuidados intensivos;
Usos *off-label*;
Fármacos no autorizados;
Niños;
Neonatos

**Utilización de fármacos en niños en cuidados intensivos: estudio de las prescripciones *off-label***

**Resumen**
*Objetivo:* Evaluar los usos *off-label* (fuera de ficha técnica [FT]) y *unlicensed* (medicamentos no autorizados específicamente para niños) en cuidados intensivos neonatales y pediátricos.
*Metodología:* Se realizó un estudio transversal en la UCINP (Unidad de Cuidados Intensivos Neonatales y Pediátricos) de un hospital público de tercer nivel de Granada, incluyéndose a todos los niños en los que se indicara al menos un tratamiento farmacológico, mediante reclutamiento consecutivo, y durante un periodo de 5 meses ($N = 81$). Las variables recogidas fueron sociodemográficas, clínicas, y medicación. Todas las prescripciones fueron clasificadas a partir de la información contenida en FT sobre uso en niños.
*Resultados:* Hubo un total de 601 prescripciones, con una media de $7{,}4 \pm 6$ medicamentos por niño. Los fármacos más empleados pertenecían a los grupos J (antiinfecciosos), N (sistema nervioso) y C (cardiovascular). Algo más de la mitad de las prescripciones fueron *off-label* (52%), fundamentalmente por emplear una dosificación distinta de la recomendada en FT (79%), seguida de diferente indicación (13,5%), edad (5%) y vía de administración (2,5%). El uso de medicamentos no específicamente autorizados en niños solo supuso el 5% de las prescripciones.
*Conclusiones:* El presente estudio aporta datos sobre este tipo de prescripciones en una UCINP española. Pone de manifiesto que el 89% de los niños tiene al menos una prescripción fuera de FT y un 22,3% al menos un uso de fármaco no autorizado para niños. Cifras elevadas, pero justificables dentro del ámbito de unos cuidados intensivos que, además, incluyen neonatos. Pero aunque muchos de los tratamientos estén protocolizados, sería deseable mejorar la evidencia disponible, así como actualizar las FT.


## Introduction

It has been estimated that less than 50% of the drugs used in children have been investigated in the pediatric population. Because of this, the treatment of such patients traditionally has been based on extrapolations referred to drugs that have been developed for adults. However, we know that the conduction of adequate clinical research is the best guarantee for safe, effective and quality treatment. The scarcity of clinical trials in children is due on one hand to the limited interest of the drug industry in this concrete patient population, and on the other to the difficulties inherent to pediatric research, which involves a number of fundamentally ethical and methodological barriers.[1] Accordingly, most therapeutic agents have not been studied in children, and the benefit–risk balance of their use is therefore often supported by only limited evidence. All this in many cases has caused quality information on pediatric recommendations to be scarce or inexistent.

The Summary of Product Characteristics (SPC) approved by the Spanish Medicines Agency (*Agencia Española del Medicamento y Productos Sanitarios* [AEMPS]) is the official document reflecting the authorized conditions of use of the medication. Based on the findings of the clinical trials made, the SPC summarizes the essential scientific information addressed to health professionals. When the information on the use of a drug in children is limited or inexistent, its prescription is made outside the corresponding licensed or authorized terms–a situation internationally known as off-label (OL) and unlicensed (UL) drug use. Unlicensed prescription is generally understood as the prescription of drugs that have not been approved for the pediatric population, while off-label prescription involves the use of drugs that have been approved for children but which are used under conditions different from those authorized in the corresponding SPC, i.e., involving different indications, doses, age ranges or administration routes. The proportion of drugs prescribed outside the authorized terms has been studied in recent years, though the results have been highly varied.[2] Most studies have been conducted on an in-hospital basis, and those carried out in neonatal Intensive Care Units (ICUs) are particularly relevant in this respect. Among newborn infants, the number of patients that receive at least one OL or UL prescription is much higher than in any other medical or surgical pediatric ward–with percentages reaching 70–97% of the patients.[3]

The use of these OL or UL prescriptions is not necessarily incorrect: it simply means that the evidence and