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ORIGINAL ARTICLE

Off-label and unlicensed drug use: Results from a pilot study in a paediatric intensive care unit☆

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Abstract
Purpose: To analyze the prevalence of use of off-label and unlicensed drugs in a paediatric intensive care unit of a University Hospital.
Method: An observational, descriptive, prospective six week pilot study in a paediatric intensive care unit. Hospitalized patients aged between 0 and 18 years were included. Each prescribed drug was evaluated taking into account indication and condition of use, according to the information available on the summary of product characteristics established by the European Medicines Agency. A sequential algorithm was defined allowing drug classification in unlicensed, off-label or approved.
Results: 42 patients were included. A total of 696 prescriptions, involving 102 different drugs, were analyzed. All patients had at least one off-label prescription, and a median of 8.9 off-label prescriptions were obtained. Of the total prescriptions, 8.6% were unlicensed and 53.9% corresponded to off-label use. The main reason for off-label use was by indication, followed by age and dose. A lineal tendency between off-label drug use and patient age was observed, where off-label use increased as patient age decreased. The drugs most commonly used off-label were: atropine, etomidate, dipyrone and ranitidine, and unlicensed drugs: spironolactone, sildenafil, acetazolamide and hydrochlorothiazide.
Conclusion: Paediatric intensive care units are characterized by a high ratio of off-label and unlicensed prescriptions. The scarce number of studies performed in this specific and complex

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sub-population added inconveniency to the current lack of data on safety and efficacy for drugs in paediatrics. Performing studies with these characteristics allowing us to document practice on paediatric drug utilization is required.

PALABRAS CLAVE
Unidad de Cuidados Intensivos Pediátricos;
Utilización de medicamentos;
Uso aprobado de medicamentos;
Uso off-label;
Indicación fuera de ficha técnica;
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Utilización de medicamentos en condiciones *off-label* y *unlicensed*: resultados de un estudio piloto realizado en una unidad de cuidados intensivos pediátricos

Resumen
Objetivo: Evaluar el perfil de utilización de medicamentos en situaciones no autorizadas en una unidad de cuidados intensivos pediátricos de un hospital universitario.
Métodos: Se realizó un estudio observacional descriptivo prospectivo durante 6 semanas en una unidad de cuidados intensivos pediátricos. Se incluyeron pacientes ingresados con edades entre 0-18 años. Se evaluó cada uno de los medicamentos prescritos, indicación o condición de uso, según la información reflejada en las fichas técnicas autorizadas por la Agencia Europea de Medicamentos. Se definió un algoritmo secuencial para clasificar de manera estandarizada los medicamentos según la condición de prescripción en *unlicensed*, *off-label* o aprobado.
Resultados: Se incluyeron 42 pacientes, analizándose un total de 696 prescripciones, que implicaron 102 fármacos diferentes. Todos los pacientes tuvieron al menos un tratamiento *off-label*. El 8,6% del total de tratamientos analizados se utilizaron en condiciones *unlicensed* y el 53,9% en *off-label*. El principal motivo de uso *off-label* fue por indicación, seguido de la edad y dosis. Existe una relación lineal entre frecuencia de uso de medicamentos en condiciones *off-label* y la edad del paciente, aumentando esta frecuencia según disminuye la edad del paciente. Los medicamentos más utilizados en condiciones *off-label* fueron: atropina, etomidato, metamizol y ranitidina, y en condiciones *unlicensed* fueron: espironolactona, sildenafilo, acetazolamida e hidroclorotiazida.
Conclusión: La unidad de cuidados intensivos pediátricos se caracteriza por un alto ratio de medicamentos prescritos en condiciones no autorizadas. La realización de estudios de estas características permite documentar la práctica clínica respecto al uso de medicamentos en condiciones distintas a las autorizadas.

Introduction

Encouraging effective and safe use of drugs in children is a current worldwide necessity. The resolution of problems associated with drug use in children has been tackled over the years. The objective is clear, to provide children with safe and effective drugs including precise and updated information. However, in spite of efforts by physicians, researchers, scientific societies and health-related policies, to date, a series of obstacles still exists, preventing an adequate development of drugs for paediatric use. These barriers are well known, and amongst them we find[1,2]: the cost of performing corresponding studies; the difficulty in designing trials; the time necessary for completing the contemplated study periods in protocols for children, far superior to those in adults; lengthy approval procedures; the complex and specific ethical aspects involved in all research concerning children; and lastly, obtaining consent from patients who cannot concede it themselves.

Due to the lack of safety and efficacy data, the ''non-approved'' use of drugs in paediatrics has always involved a risk for patients. The drugs used, following the label specifications established at the beginning of commercialization have a lower tendency towards producing adverse effects than those drugs whose use in children is not authorized or is prescribed in different conditions to those stated on the label.[3–9] This was revised by the European Medicines Agency (EMA) itself, concluding that the use of ''non-approved'' drugs increments the incidence and severity of adverse reactions.[10] Nevertheless, as the percentage of drugs without paediatric indication is so high (50–90%) and affects approximately 20% of the European Union population (around 150 million people under 18 years),[2] the use of drugs in these conditions is almost obligatory. It is important that children are not denied access to clearly beneficial drugs. It is neither practical nor appropriate to restrict use only to drugs approved for this age group. Health professionals are obliged to give children the best possible treatment, which invariably implies non-authorized drug use or use in conditions different to those approved.[7,11,12]

The aims of the present study were to characterize unlicensed and off-label drug prescription and analyze its