USE OF OFF-LABEL MEDICINES IN PEDIATRIC POPULATION

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Abstract: Modern use of drugs in the treatment of diseases of children and newborns is increasingly based on off-label use of drugs. The lack of adequate formulations for the pediatric population, the lack of appropriate therapeutic parallels for the treatment of children's diseases and the small number of clinical trials involving the pediatric population have contributed to the mass use of these drugs. The use of these drugs implies extrapolation of doses and indications registered for adults to children, although it is known that the pharmacodynamics and pharmacokinetics of children and adults differ significantly. In the past two decades, many legislative and regulatory initiatives have been taken around the world to improve the use of drugs in children. However, children are still prescribed off-label and unlicensed drugs.
The aim of this study was to present a review of the literature in which off-label and unlicensed use in the pediatric population was investigated. Literature was searched through the Google Scholar and Pub Med search engines and using the keywords off label drug, pediatric medicine, use in pediatrics, in the period from May to August 2019. Selected and presented in this article are studies published in the period from 1996 to 2015, which as a subject of research had the use of off-label and unlicensed drugs in the pediatric population. Medicines prescribed for children should be registered for use in the pediatric population and used in accordance with approved indications for children, whenever possible. It is necessary to take measures for more rational use of medicines in pediatrics, which include the collaboration of health workers in order to provide medicines for children that are proven to be effective, high quality and safe to use.

INTRODUCTION

The use of a medicinal product in accordance with the marketing authorization, which defines the formulation, dosage, age, and issued by the relevant regulatory body, is called the use of the medicinal product in accordance with the on-label marketing authorization. The purpose of authorizing a medicinal product is to ensure that the medicinal product is tested for its efficacy, safety and quality. When the drug is prescribed outside the examined indications, the therapy may be less safe, effective and reliable, because it is based exclusively on assumptions and extrapolation. The justification for prescribing these drugs, especially in the pediatric population, due to the large differences between children and adults, even between children of different ages, in terms of pharmacodynamic and pharmacokinetic responses to the drug, is being examined.

Recently, the use of a drug that does not comply with the approved guidelines related to the indication, age, dosage regime or route of administration is becoming more common. Off-label use of drugs includes the use of drugs in higher or lower doses, use for indications not described in the summary of product characteristics, use in children outside the range of years defined by the license, use of alternative routes of administration and use of drugs in indications when contraindicated for a given drug. The use of off-label drugs is mainly related to prevention, diagnosis or therapeutic measures that are in accordance with the relevant legislation, with the primary goal of improving or improving the health condition.

Off-label use of drugs should be distinguished from the use of drugs without a license (off-license). Unlicensed use of drugs is considered to be the use of a drug that is not registered in the Republic of Serbia, but is in other countries, or that is registered, but it should be translated into another formulation or drug that is not registered (eg. for the treatment of rare diseases). Unregistered medicines are medicines that have not been approved by the regulatory body for marketing. Off-label use is considered to be the use of a drug in a way different from the manner described in the marketing authorization: use of the drug for the treatment of an indication not listed in the

summary of product characteristics, use of the drug in the age group outside the permitted range, use of the drug doses of the drug characteristics listed in the summary.

The most common reasons for the use of unregistered drugs are modifications of registered drugs (crushing the tablet to form a suspension), drugs that are registered for use in adults, but the formulation for use in pediatrics requires a special drug permit (adult drug is used in minor doses for children), new drugs that require special permission from the manufacturer (eg. caffeine injection used in case of apnea due to lung immaturity). Use of drugs outside the marketing authorization includes the use of drugs in higher or lower doses, use for indications not described in the summary of product characteristics, use in children outside the age range defined by the license, use of alternative routes of administration and use of drugs in indications when contraindicated allow for a given drug.

Modern use of drugs in the treatment of diseases of children and newborns is increasingly based on the use of off-label drugs due to lack of adequate formulations for the pediatric population, lack of appropriate therapeutic parallels for the treatment of children and almost no clinical trials involving the pediatric population [1-4].

The thalidomide catastrophe (phocomelia in newborns) and the effect of the use of chloramphenicol in children (gray baby syndrome) initiated the process of testing and registration of drugs [5]. The main goal of drug registration is to ensure that the drug is quality, safe and effective. Unfortunately, large number of medicines for children do not have a marketing authorization or marketing authorization [6]. This suggests that for many drugs used in children, evidence derived from pharmacokinetics, adequate dosing, or formulation-related studies is lacking [7,8]. Focusing on other factors influencing the pharmacokinetics and pharmacodynamics of drug dosing has received little attention during drug development in children. As a result, many drugs have been used outside of their licensed recommendations, commonly known as off-label prescribing, which has become an increasingly common prescribing trend in children. Over-the-counter prescribing for children is widespread mainly in systemically administered drugs, but also in locally applied drugs [9].

Several factors leading to off-label prescribing in children have been identified in the past. Subsequently, legislative, regulatory, governmental, and professional initiatives were introduced and implemented globally to obtain better data on the effects of drugs on children and consequently to instruct health professionals to use quality drugs that are effective for children and do not cause harm when used. Initiatives to improve drug use in children were first implemented in the United States from 1994 to early 2000. [10-13]. Almost a decade later, other countries (European Union, Canada, Australia, Japan, China and Korea) as well as international institutions (World Health Organization and the International Council for the Harmonization of Technical Requirements for Pharmaceutical Medicines for Human Use) have joined [14]. Data from the literature show that most initiatives taken in the past have been aimed at encouraging increased research on the use of drugs in children, in order to improve the registration process and enable the safe use of drugs in the pediatric population.

However, despite numerous global initiatives, the number of clinical trials conducted in children is still insufficient, ie. the use of drugs in children is rarely based on evidence from clinical trials [15].

The aim of this study is to provide an overview of the global trend and prevalence of prescribing off-label drugs from 1996 to 2016, and to suggest future directions related to studies related to off-label prescribing in children.

METHODOLOGY

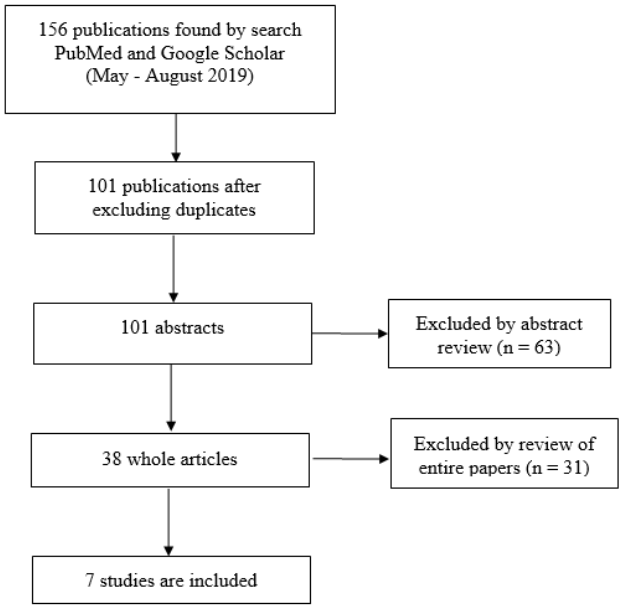
Data collection was performed by electronic search of the PubMed index database and Google Scholar. The literature search and selection protocol has been defined using the PRIZMA method [16]. The corresponding flow diagram is graphically shown in Figure 1. The search was performed in the period from May to August 2019. Selected and presented in the paper are studies published in the period from 1996 to 2015. Searched keywords are: off label drug, pediatric medicine, use in pediatrics. Original research was included which provided data on the extent of use of off-label and unlicensed drugs in the pediatric population as well as one systematic review.

Criteria for inclusion were: 1) published texts in full text in the period from January 1996

to December 2016; 2) articles in Serbian and English; 3) studies showing data on the results of the prevalence of prescribing drugs outside the use permit for children; 4) off label use of cardiac, respiratory, antiallergic, oncological, analgesic drugs and antibiotics

Exclusion criteria were: 1) notes and conferences; 2) off label use of other therapeutic groups of drugs. The title and summary of the articles have been carefully examined to determine the inclusion of the study in this review. The following information was extracted from the eligible studies: 1) study identification; 2) study details (study design, setting, study period, method); 3) defining off-label drug administration; 4) source references; 5) quantification of outcomes; 6) results

Figure 1. PRIZMA diagram



RESULTS AND DISCUSSION

During the research, 101 studies were identified, of which 7 were presented in this article, with the aim of presenting off-label use of drugs in different therapeutic groups: cardiac, respiratory, antiallergic drugs, antibiotics, oncology drugs and analgesics.

In a study conducted at the Department of Pediatric Cardiology, 544 patients participated in the University Children's Hospital in Belgrade and included 2,037 prescriptions, with 102 different drugs, of which 41% were registered drugs, 11% unregistered and 47% prescribed drugs. off -label. Drugs are prescribed off-label: due to age 21% and due to a different dose 26%. The largest number of unregistered and off-label drugs (72%) is prescribed to children aged between 2-11 years. Katopil is the only registered ACE inhibitor for use in the pediatric population and is one of the most prescribed drugs in this study, with one-third of prescriptions being prescribed off-label in relation to the dose of katopil [17].

In a national cohort study conducted in Italy, in the period 2002-2006, medical records of children under 14 years of age were analyzed, and the degree of prescribing drugs belonging to the ATC code R03 - ß mimetics, inhaled glucocorticoids, inhaled anticholinergics, combined formulations, antiallergic drugs, xanthines and leukotriene receptor antagonists. 90% of R03 prescriptions included 11 active substances or combinations. Inhaled glucocorticoids are the most prescribed off-label, with 19% in terms of age and 56% in terms of indications for use. The largest number of off-label drugs was in children younger than 2 years [18].

In the cohort study, conducted in the Netherlands, the largest number of prescribed drugs - off-label and unregistered - was also the largest in the group of children aged 1 month to

2 years. The one-year cumulative risk of off-label and unregistered drugs is 45%, among children with at least one prescription for a respiratory drug [19].

In a prospective study, which lasted from February to March 2000, at the Children's Clinic in Great Britain, in the intensive care and acute care wards, analgesics used in children were classified into those used in accordance with the marketing authorization and those are applied off-label, in accordance with the valid drug registries in the UK. The study included 715 prescriptions, of which 67% were licensed drugs, prescribed in accordance with the summary of product characteristics, and 33% were licensed drugs, but prescribed outside the use permit. Diclofenac, pethidine and morphine are mostly prescribed off-label, while drugs are most often prescribed off-label, in terms of dose. The high percentage of off-label use of this drug, shown in this study, is explained by the fact that diclofenac is not approved for pain therapy in children, but that it has been shown to be effective in adults intra- and postoperatively [20].

The Morais-Almeida M study (2013) showed that the most prescribed off-label drugs were nasal corticosteroids, 76% of the total number of prescription drugs [21], while 22% were off-label antihistamines. In other studies, off-label administration of antihistamines varied between 4.5 -43%. Cetirizine, levocetirizine and loratadine have been most studied in terms of long-term safety when used in the pediatric population. Despite pharmacokinetic studies conducted for next-generation antihistamines, long-term safety studies in children are lacking [22].

A study conducted in three European countries, Italy, Great Britain and Greece, evaluated the off-label use of antibiotics, as the most frequently prescribed drugs for children. The number of prescribed drugs with an unregistered dose was high in all three countries in the neonatology departments, but the number was significantly higher in Italy compared to the United Kingdom. Antibiotics that are most often prescribed outside the recommended dose are aminoglycosides, specifically amikacin and gentamicin. The most common clinical indication for use outside the recommended range is suspected or confirmed diagnosis of sepsis, although significant use of drugs outside the recommended doses in medical prophylaxis was more common in Italy and Greece, compared to the United Kingdom. The most frequently prescribed antibiotics prescribed outside the registered indication are fluoroquinolones in Great Britain and ampicillin and gentamicin in Italy and Greece, while the most common indications were suspected sepsis or diagnosed sepsis.

In the pediatric ward, antibiotics most commonly prescribed outside the registered dose are amoxicillin clavulanate in Italy, cefuroxime in Greece, and gentamicin in the United Kingdom. Doses were higher than recommended in Italy and Greece and lower than recommended in the UK. The most common dosages outside the registered recommendations were indications - sepsis, lower respiratory tract infections and surgical prophylaxis in all three countries, regardless of prevalence. Off-label in terms of dose was most common in the group of children aged 28 days - 23 months [23].

The use of anticancer drugs is precisely described in the drug authorization in terms of the type or subtype of the tumor and the length of treatment. Prescribing anticancer drugs is believed to be often prescribed outside the use permit, while a small number of studies have been conducted, in order to obtain a realistic state. Prospective studies, conducted between 1990 and 2002, indicated a proportion of off-label drug use in children and adults. Most off-label drugs were for palliative care of patients, some were associated with a better clinical effect and in the treatment of specific tumors, they were part of standard therapy [24].

Table 1: Tabelar view of studies presented in this article

Authors/ Article/ Year	Study	Aim of the study	Methods	Results
Bajcetic et al./Eur J Clin Pharmacol/ 2005	Off-label and unregistered drugs in pediatric cardiology	Scope and nature of prescribing off-label drugs in pediatric cardiology, in hospitalized patients	Prospective study; patient records	The problem of off-label and unregistered drugs is in line with the lack of adequate formulations globally
Jong, Eland et al./ Eur Respir J/2004	Unregistered and off-label resorption drugs prescribed to the pediatric population	Unregistered and off-label respiratory drugs prescribed to children, the Netherlands	Cohort, national study; data were collected from a computerized database of children's medical records	A large percentage of respiratory drugs prescribed to children are unregistered or registered but prescribed off label
Baiardi et al./Acta Pediatrica/ 2009	Use of the drug in accordance with the marketing authorization and off-label use of respiratory drugs in the pediatric population in Italy	To determine the degree of prescription of respiratory drugs (ATC code: R03) in Italy and to assess the extent of use of off-label drugs, in relation to the dose or indication	Cohort study	There is a need to conduct quantitative studies, with the aim of increasing current knowledge about registered medicines and to review the registration process and regulatory procedures in order to reduce off-label use of medicines
Conroy et al /Peadiatric Anaesthesia/ 2001	Use of off label and unregistered analgesics in the management of pain therapy in pediatrics	Document the incidence and nature of the use of unregistered and off-label analgesics in children	Prospective study; a questionnaire was used as a tool	67% of drugs were registered; 33% is registered, but the application is off-label; the study did not identify the use of unregistered drugs
Silva et al./ WAO Journal/ 2014	Prescribing off-label drugs in the treatment of allergic diseases in children	A review of the literature aimed at describing and discussing the off-label use of drugs in the therapy and control of allergic drugs in children	Review article	There is a need for a new proposal to highlight the priority for pediatric clinical research, which could meet all the needs of the pediatric population, especially in the field of allergies and respiratory diseases.
Porto et al./Eur J Clin Pharmacol/ 2010	Use of antibiotics off-label in three European countries in children	The aim was to evaluate off-label antibiotic use in three European countries - the UK, Italy and Greece	Antibiotic prescriptions were evaluated for all hospitalized patients in the neonatal intensive care unit: 2 hospitals in the UK, one hospital in Italy and one hospital in Greece	Off-label drug use is usually dose- or indication-related, rarely for years. the only antibiotics identified that have been used off the label, and related to age are: meropenem for neonatal and quinolones and linezolid for older children, which is a priority for future studies
Leveque /Lancet Oncol/ 2008	**Off-label use of anticancer drugs**	**The scope of off-label prescribing of oncology drugs**	**A review of prospective studies in the period 1990-2002**	**Percentage of off-label drug use in children and adults 6-33.2%**

CONCLUSION

According to the analysis of the literature, the prevalence of prescribing off-label and unregistered drugs in the pediatric population is evident and very widespread in the past in intensive care units.

Medicines prescribed for children should be registered for use in the pediatric population and used in accordance with approved indications for children, whenever possible. Although there are indications that the use of off-label and unregistered drugs has more benefits than the risk that the use of that drug poses, this leads to an increasing use of these drugs even when such use is not justified, ie. it may be less effective or harmful.

The lack of indications for use in children, in relation to the dose or inadequate formulation for the pediatric population may prevent children from receiving effective therapy or may lead to errors in the routes of administration of the drug.

The increase in the prevalence of off-label drug use suggests that legislative, regulatory initiatives are not sufficient to improve drug use in children. Aspects of behavior and knowledge related to off-label prescribing as well as efforts to integrate evidence into practice must also be assessed and consolidated as part of a joint effort to reduce prescribing gaps for children.

It is necessary to take measures for a more rational use of medicines in pediatrics, which include the collaboration of health workers in order to provide medicines for children that are proven to be effective, high quality and safe to use.

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