Allergol Immunopathol (Madr). 2014;42(4):342–347

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

ORIGINAL ARTICLE

Off-label prescribing for allergic diseases in pre-school children

M. Morais-Almeida*, **A.J. Cabral**

Immunoallergy Department, CUF Descobertas Hospital, Lisbon, Portugal

Received 29 December 2012; accepted 2 February 2013
Available online 14 June 2013

KEYWORDS
Asthma;
Atopic eczema;
Infant;
Off-label prescription;
Pre-school children;
Rhinitis

Abstract
Background: Several studies have demonstrated that medication is commonly used off-label in children with allergic diseases. The aim of this study was to characterise off-label use of prescriptions for allergic diseases in pre-school children from an allergology outpatient unit.
Methods: The clinical files of children aged ≤6 years seen in a reference allergology consultation with asthma, allergic rhinitis, and/or atopic eczema were reviewed. A total of 500 patients were consecutively observed from January to June 2012. The data collected included gender, age, diagnosis, and prescriptions with the respective daily dosage.
Results: A total of 1224 prescriptions were registered. The most prescribed medications were oral antihistamines (34.6%), antileukotrienes (22.6%), topical nasal corticosteroids (20.3%), and inhaled corticosteroids (17.7%). From all prescriptions, 422 (34.5%) were considered off-label for age (62.6%), dosage (31.7%), or clinical indication (5.7%). Off-label use was more frequent in children aged <2 years, with 73.5% prescribed for children of this age.
Conclusions: Off-label use of drugs for the treatment of paediatric allergic diseases is high. However, these prescriptions are not necessarily wrong, and are recommended in many guidelines. Randomised controlled studies are limited by methodological difficulties creating the need for more observational studies in order to further evaluate the safety and efficacy of drugs used in children.

Introduction

Many drugs used in the treatment of allergic diseases are not appropriately studied in the paediatric population, especially in infants and younger children. Nonetheless, their off-label use, i.e. use outside the formal indications authorised by the regulatory authorities, in a different age group, dose, or indication[1] is common in many paediatric illnesses like allergic disease. This happens because of practical and ethical considerations in carrying out clinical trials in this population.[2] In general, off-label prescription rates range from 11% to 37% in children treated in the community setting, and in up to 62% of children in paediatric hospital wards.[3] The major concern with this off-label use is the increased risk of adverse drug reactions.[4] Additionally,

* Corresponding author.
E-mail address: mmoraisalmeida@netcabo.pt (M. Morais-Almeida).

0301-0546/$ - see front matter © 2012 SEICAP. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.aller.2013.02.011

Table 1 Drugs used for treatment of asthma, allergic rhinitis, and atopic eczema, and their authorizations for use according to age and dose.

Category	Drug	Minimum age	Maximum dose
IC	Budesonide	2 years	400 μg/day – 2 to 7 years
	Fluticasone	12 months	200 μg/day – 1 to 4 years; 400 μg/day – 4 to 16 years
NC	Budesonide	6 years	400 μg/day
	Fluticasone furoate	6 years	55 μg/day
	Mometasone	6 years	100 μg/day
LABA[a]	Salmeterol	4 years	100 μg/day
AH	Cetirizine	2 years	5 mg/day – 2 to 6 years; 10 mg/day – 6 to 18 years
	Levocetirizine	2 years	2.5 mg/day – 2 to 6 years; 5 mg/day – older than 6 years
	Loratadine	2 years	5 mg/day – 2 to 6 years; 10 mg/day – 6 to 18 years
	Desloratadine	12 months	1.25 mg/day – 1 to 5 years; 2.5 mg/day – 6 to 12 years
	Ebastine	2 years	2.5 mg/day – 2 to 5 years; 5 mg/day – 6 to 11 years
	Ketotifen	6 months	0.1 mg/kg/day - 6 months to 3 years; 2 mg/day – older than 3 years
AL	Montelukast	6 months	4 mg/day – 6 months to 5 years; 5 mg/day – 6 to 14 years
TI	Pimecrolimus	2 years	

Source: Infarmed, I.P.[11]
IC: inhaled corticoids; NC: nasal topic corticoids; LABA: long acting β2 agonists; AH: oral antihistamines; AL: anti-leukotriene; TI: topic immunomodulator.
[a] Always used in combination with fluticasone – authorisations identical to isolated use.

younger children and infants have a considerably increased risk of prescription errors, especially dosage errors.[5]

However, off-label prescriptions are not necessarily incorrect,[6] and may even be appropriate in certain clinical situations provided there is no alternative treatment, and when the likely benefits outweigh the potential risks,[7] such as when conventional treatments are unable to achieve control of the disease. The potential advantages of off-label prescribing, apart from the probable benefit to the individual patient, are that new therapeutic uses may be described, and data on the efficacy and safety of the drug being used in new settings may be collected.[8] With off-label prescriptions, the physician must act as an enlightened intermediary. On the one hand, managing the regulatory data aimed at ensuring the effectiveness and safety of the prescription, and on the other hand, putting all his or her knowledge into serving the interests of the patient.

Several studies have consistently shown that off-label use in children is common. A population-based cohort study carried out in primary care units in Holland assessed the prescribing of respiratory drugs in 2502 children, showing that almost 37% were off-label, and 39% in this group were prescriptions for asthma.[9] The TEDDY study, comparing the use of anti-asthmatic drugs in children in Holland, Italy, and the United Kingdom, established that off-label use of β2-agonists and inhaled corticosteroids is frequent, including up to 80% of the inhaled budesonide prescriptions in Italy.[10]

In Portugal, few studies exist concerning off-label use of drugs in paediatric populations, and none are specifically related to drugs for the treatment of allergic disease. This study aimed to characterise off-label prescribing of drugs used in the treatment and control of asthma, allergic rhinitis, and atopic eczema in a significant sample of pre-school aged children followed by allergy specialists at a reference allergology consultation.

Methods

The clinical files of children aged ≤6 years followed in our allergology consultation who were diagnosed with current asthma, allergic rhinitis, and/or atopic eczema phenotypes, with predominantly moderate to severe clinical presentations, were systematically reviewed. Consecutive medical visits were analysed from the beginning of January 2012 until the inclusion of a total of 500 patients (June 2012).

The data collected included gender, age, diagnosis, and drugs prescribed for the control of allergic diseases that were used for a minimum period of two weeks, as well as the respective dosages. Drugs used for acute treatment were not considered. The drugs included were classified as follows: (1) inhaled corticosteroids (IC); (2) nasal topical corticosteroids (NC); (3) long acting β2 agonists (LABA); (4) oral antihistamines (AH); (5) oral antileukotrienes (AL); (6) topical immunomodulators (TI).

The formal indications for each drug were available from *Infarmed – Autoridade Nacional do Medicamento e Produtos, I.P.* (Infarmed),[11] the national authority on drug control and authorisation, and were confirmed by the pharmaceutical companies responsible for their production and distribution; these indications were systematically compared by the authors, who found no discrepancies (Table 1).

The age groups were classified according to the paediatric age definitions provided by the *European Medicines Agency* (EMA).[12] As such, the sample was divided as follows: age < 2 years, and age 2–6 years. Although EMA considers an age group for newborns ''younger than one month old'', the sample did not include any patients in this age group.