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Unlicensed and off-label prescription of respiratory drugs to children

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Unlicensed and off-label prescription of respiratory drugs to children. G.W. 't Jong, I.A. Eland, M.C.J.M. Sturkenboom, J.N. van den Anker, B.H.C. Stricker. ©ERS Journals Ltd 2004.

ABSTRACT: Many respiratory drugs are not available in formulations suitable for infants and toddlers. Efficacy and safety research is mostly restricted to older children. However, respiratory drugs are frequently used in children for common diseases like asthma, upper and lower respiratory tract infections, rhinitis and sinusitis. The unlicensed and off-label use of respiratory drugs in children were studied.

A population-based cohort study was conducted by using the computerised medical records in the Integrated Primary Care Information project. The study population comprised a random sample from all children aged 0–16 yrs who were registered with a general practitioner in 1998. All prescriptions for respiratory drugs during the study period were classified according to their licensing and off-label status.

The study population comprised 13,426 patients (51.7% male, median age 8.7 yrs), of whom 2,502 (19%) received 5,253 prescriptions for respiratory drugs in 1998. A total of 3,306 (62.9%) prescriptions concerned licensed drugs. Of the remaining 1,947 prescriptions (37.1%), 882 (16.8%) were unlicensed for use in children, and 1,065 (20.3%) were prescribed off-label. The 1-yr cumulative risk of receiving an unlicensed or off-label prescription was 45% among children with at least one prescription for a respiratory drug.

This population-based study showed that a large proportion of respiratory drugs prescribed by the general practitioner are unlicensed for use in children, or licensed but prescribed in an off-label manner. Results have to be interpreted with caution because they may unjustly suggest inaccurate prescribing, whereas it may be difficult to treat children with respiratory symptoms and diseases, because for many respiratory drugs paediatric data on safety and efficacy are insufficient. These findings underline the importance of research on suitable formulations, dosages and efficacy of respiratory drugs in children.

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The extent and nature of unlicensed and off-label drug prescription in paediatric clinical care has been the subject of several surveys in Europe [1–7] and these consistently showed that a very large proportion of prescribed drugs are either unlicensed for use in children or used outside the terms of the product license ("off-label"). Several studies also provide information on the extent of this type of drug prescription in children with respiratory diseases, but information provided is often limited.

Respiratory drugs are used for several of the most common paediatric diseases such as asthma, upper and lower respiratory tract infections, rhinitis and sinusitis; conditions that are treated in general practice rather than in clinical care [8–12]. Previous research by the present group revealed that 70% of available respiratory drugs in the Netherlands are not fully licensed for use in children, and many of these (80%) are registered only for specific age/weight groups [13]. Many of the children with respiratory problems present themselves long before they have reached the age range given in the product information of many respiratory drugs. As part of a larger project [14], a large cohort study was conducted in general practice to assess the extent and nature of unlicensed and off-label prescription of respiratory drugs in children.

Methods

Setting

All data were retrieved from the Integrated Primary Care Information (IPCI) project, a longitudinal observational database with data from computer-based patient records from a group of 150 general practitioners (GPs) in the Netherlands. As of 2001, the IPCI database contains data on a cumulative number of 485,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research [15].

Design

A population-based cohort study was conducted in a dynamic population of children in the IPCI database who were permanently registered with one of the participating general practices between 1 January 1998 and 31 December 1998 [14]. In 1998, 53,702 children were registered in the IPCI database. Since this research required manual review of all prescriptions 25% were randomly sampled from the population,

which formed the primary study population (n=13,426). All study subjects were followed from 1 January 1998, or the date of registration in the GP practice, whichever was latest, until the earliest of one of the following censoring points: death, reaching the age of 17 yrs, transferring out of the practice, or end of the study period.

Classification of prescriptions

From the prescription file, all prescriptions plus their dosage regimens and indications issued to the primary study population in 1998 were extracted. Respiratory drugs were categorised into "nasal preparations" (ATC R01), "oropharyngeal preparations" (ATC R02), "antiasthmatics" (ATC R03), "cough and cold medications" (ATC R05) and "antihistamines for systemic use" (ATC R06).

All prescriptions for respiratory drugs were classified regarding their licensing status [3]. The main mutually exclusive categories were: 1) licensed for children; 2) licensed, but used off-label; and 3) unlicensed for children. Further classification of prescriptions was performed as described earlier [14]. As a reference source for classification, the official product license was used, as approved by the Dutch Medicines Evaluation Board and the European Medicines Evaluation Agency (EMEA).

Age was classified in line with the paediatric age definitions provided by the EMEA [16], but the category 2–<12 yrs was split because of heterogeneity within this age group [17]. Age groups used were: 0–<1 month, 1 month–<2 yrs, 2–<6 yrs, 6–<12 yrs, and ⩾12 years. Since the number of prescriptions in the youngest age group was negligible (n=1), this group was excluded from further analysis.

Analysis

Descriptive analyses were conducted for patient demographics, prescription data and outcome. Statistical comparisons consisted of independent unpaired t-tests for continuous variables, and Chi-squared tests for discrete variables. Confidence intervals (CI) of 95% around prevalence estimates were based on the normal distribution.

Table 1. – Characteristics of study population

Variable	Respiratory drug prescription-receiving children	Drug prescription-receiving children[¶]
Subjects	2502	6313
Male	1318 (52.7)	3066 (48.6)
Female	1184 (47.3)	3247 (51.4)
Age groups[#]		
0–<1 month	1 (<0.1)	40 (0.6)
1 month–<2 yrs	821 (32.6)	1263 (20.0)
2–<6 yrs	947 (37.8)	1797 (28.5)
6–<12 yrs	833 (33.3)	1921 (30.4)
⩾12 yrs	552 (22.0)	1562 (24.7)

Data are presented as n (%) unless otherwise stated. Percentage is calculated based on column total. [#]: totals do not add up to the total of the study group, since some patients contributed to several age groups; [¶]: all drug prescriptions over 1998, including respiratory drugs.

Results

During the study period, 5,253 prescriptions concerning respiratory drugs were issued to 2,502 patients (table 1). The median number of respiratory drug prescriptions among respiratory drug-using children was 1 (interquartile range (IQR) 1–2). The median number of prescriptions was 2 per patient per year (IQR 1–3) for antiasthmatics. Patients who received respiratory drugs were significantly younger than the rest of the study population ($p<0.001$).

The most frequently prescribed respiratory drugs were antiasthmatics (40.7% of all prescriptions), followed by systemic antihistamines (27.7%) and nasal preparations (23.2%). Largest subclasses of drugs (in numbers of prescriptions) were corticosteroids (18.0%), selective β_2-sympathomimetics (17.1%), systemic antihistamines (14.8%), sympathomimetics for nasal use (12.7%) and phenothiazine derivates (8.9%), as shown in table 2. The most frequently prescribed drugs were salbutamol (12.7%), xylomethazoline (12.7%), promethazine (7.4%), beclomethasone (6.5%) and fluticasone (6.5%).

Of the 5,252 prescriptions, 3,305 (62.9%) were licensed for use in children, and prescribed in concordance with the product license. Of the remaining 1,947 prescriptions (37.1%),

Table 2. – Respiratory drug utilisation

Drug class	Drug category	Prescriptions						Users			
		Total	%[#]	UL	%[¶]	OL	%[¶]	Total	%[#]	UL/OL[+]	%[¶]
Inhaled corticosteroids	Antiasthmatics	943	18.0			307	32.6	488	3.6	180	36.9
Inhaled β_2-sympathomimetics	Antiasthmatics	898	17.1	162	18.0	300	33.4	561	4.2	318	56.7
Indifferent antihistamines[§]	Antihistamines for systemic use	776	14.8	299	38.5	49	6.3	517	3.9	267	51.6
Nasal sympathomimetics	Nasal preparations	668	12.7	32	4.8	9	1.3	602	4.5	37	6.1
Pheothiazine derivates	Antihistamines for systemic use	467	8.9	73	15.6	20	4.3	389	2.9	78	20.1
Nasal corticosteroids	Nasal preparations	276	5.3	141	51.1	4	1.4	182	1.4	94	51.6
Nonsteroid antiallergic drugs	Nasal preparations	200	3.8	119	59.5	4	2.0	120	0.9	75	62.5
Piperazine derivates	Antihistamines for systemic use	175	3.3	15	8.6	7	4.0	119	0.9	15	12.6
Opium alkaloids and derivates	Cough and cold medications	164	3.1	1	0.6	26	15.9	141	1.1	25	17.7
Parasympathomimetics	Antiasthmatics	112	2.1	7	6.3	100	89.3	88	0.7	84	95.5
Expectorants	Cough and cold medications	98	1.9	34	34.7	20	20.4	93	0.7	74	79.6
Mucolytics[f]	Cough and cold medications	81	1.5			28	34.6	71	0.5	26	36.6
Other drugs for nasal use[##]	Nasal preparations	75	1.4					57	0.4		
Other cough-suppressant drugs[¶¶]	Cough and cold medications	75	1.4			52	69.3	61	0.5	44	72.1
Sympathomimetics+other antiasthmatics[++]	Antiasthmatics	69	1.3			68	98.6	50	0.4	50	100.0

UL: unlicensed; OL: off-label. [#]: percentage of total number of respiratory prescriptions (n=5252) and patients in the cohort (n=13426); [¶]: row percentage; [+]: patients with an UL or OL prescription; [§]: *e.g.* deptropine, ketotifen, and tefenadine; [f]: acetylcysteine and brome hexin; [##]: *e.g.* mupirocin and NaCl; [¶¶]: *e.g.* pentoxyverine; [++]: *e.g.* fenoterol+ipratropium in Berodual®.

Table 3. – Number of drug prescriptions within licensing status

Variable	Unlicensed/ off-label	Licensed
Age groups		
1 month–<2 yrs	644 (65.2)	343 (34.8)
2–<6 yrs	583 (35.2)	1074 (64.8)
6–<12 yrs	422 (27.9)	1089 (72.1)
⩾12 yrs	298 (27.2)	799 (72.8)
Drug classes		
Antiasthmatics	1008 (47.1)	1131 (52.9)
Antihistamines for systemic use	466 (32.0)	991 (68.0)
Nasal preparations	309 (25.3)	910 (74.7)
Cough and cold medication	162 (38.1)	263 (61.9)
Oropharyngeal preparations	2 (15.4)	11 (84.6)
Total	1947 (37.1)	3305 (62.9)

Data are presented as n (%). The percentages are within age group/drug class.

882 (16.8%, 95% CI 15.8–17.8) were prescriptions for unlicensed drugs, and 1,065 (20.3%, 95% CI 19.2–21.4) were off-label prescriptions for licensed drugs. Unlicensed drugs consisted of modification of preparations (8.7%), drugs that lacked information on use in children (6.6%), and drugs that were contraindicated for use (1.4%). Prescriptions were off-label for age (7.3%), dose (7.8%), frequency (3.8%), indication (4.5%) or dosage form (1.1%). Drugs could be off-label for several reasons. Unlicensed and off-label drug use differed for the various respiratory drug classes (table 2). Off-label use was especially high for antiasthmatic drugs (39%), and cough and cold medication (30%). Antiasthmatic drugs were frequently off-label for dose and/or indication or age/weight (14, 10 and 15%, respectively), and cough and cold medication was mostly off-label for dose (19%). Unlicensed use was especially high for nose preparations and antihistamines for systemic use (24.0 and 26.4%, respectively), but off-label use was very low in these groups; the primary reason for unlicensed drug use for both drug classes was modification of preparations by the pharmacy. The most frequently prescribed unlicensed and off-label drugs were salbutamol (inhaled, off-label for age and dose), deptropine (syrup, unlicensed), fluticasone (inhaled, off-label for dose), terbutaline (inhaled, off-label for dose), and sodium cromoglycate (nasal spray, no information on use in children).

The numbers of unlicensed and off-label prescriptions were highest in the age group 1 month–<2 yrs (table 3). The 1-yr cumulative risk of an unlicensed or off-label prescription was 45% (95% CI 43–47) among children with at least one prescription for a respiratory drug. Males had a 15% (95% CI 6–25) higher chance of receiving unlicensed or off-label prescriptions for antiasthmatics than females. For other groups no significant differences were found.

For some infrequently used drugs (parasympathomimetics and expectorants), the percentage of exposed children with at least one off-label or unlicensed prescription was highest (95 and 79%, respectively). However, the percentage of children with at least one off-label or unlicensed prescription was also high among the drugs with the highest exposure (table 2).

Discussion

This study showed a high 1-yr cumulative risk of unlicensed and off-label use of respiratory drugs among children who use these drugs. In terms of prescription, 17% were unlicensed and 20% off-label. The risk of at least one off-label or unlicensed prescription was highest among users of parasympathometics, expectorants, sympathomimetics for inhalation and systemic antihistamines, and was highest for young children.

These high numbers of unlicensed and off-label drug use, however, have to be interpreted with caution because they may unjustly suggest inaccurate prescribing. In fact, there is a lack of properly licensed drugs for all age groups in dosage forms that are suitable, and with dosing windows that correspond to the needs regarding symptom relief and cure of patients. Another reason for a cautious interpretation is the fact that there may be a difference between the product information and prescribing guidelines, such as given by the Dutch College of General practitioners and in formularies like the *Physician's Desk Reference* [18], and the *British National Formulary* or the *Medicines for Children* formulary [19]. Therefore, not all deviations from the product information can be qualified as errors. However, the licensing information text of many respiratory drugs provides physicians with dosage recommendations that are more restricted than the information text in common drug formularies, which also contain data that are based on experience, and not so much on evidence.

The high percentage of modified preparations for children (8.7%) is a direct result of the lack of licensed paediatric formulations [20, 21], which requires modification of commercial preparations in the pharmacies. The drug prescriptions that were off-label for age were not checked for other off-label categories like indication and dosage, since these were not provided in the labelling information text. The dosage form therefore seems to be correct for most prescriptions, but especially in the younger children, the availability of suitable formulations is limited. Although there have been major advances in relation to different types of inhalers for children of different ages with asthma, such as the turbohaler, nebuhaler and volumatic inhaler [22], knowledge of reproducibility of dose and lung disposition is limited [23]. Pressurised metered dose inhalers/spacers and face masks are needed for these children [24], and parents have to be adequately instructed to be able to apply the drug. Dose variability for these drugs in small infants is large, and increased by complicating factors like bad cooperation by the wheezy infant [25].

Earlier research on unlicensed and off-label respiratory drug use in general practice in children is scarce, except for a study in the UK [26] that reported individual percentages of unlicensed and off-label use for some respiratory drugs. However, this study group was small, since only one GP participated. Besides, the classification system used by McIntyre *et al.* [26] for unlicensed and off-label status of drugs differs from the system that was used for this study.

A recent study in the Netherlands based on pharmacy dispensing records showed that 15.1% of prescriptions in that study were off-label, and another 6.4% unlicensed. Prescriptions by specialists (outpatient), prescriptions for new drugs, prescriptions for drugs with a low use in the paediatric population, and prescriptions for infants were risk factors for using a systemic drug unlicensed or off-label in that study [27]. Since the indications are not available in pharmacy dispensing data, the indication for prescription of a drug was not evaluated. The prescriptions in this study were also not evaluated for dose, frequency, dosage form and route of administration. Therefore, the results show a much lower unlicensed and off-label use of drugs in children. However, the authors acknowledge the risk factors as indicated by this article. Unfortunately, they were unable to differentiate between outpatient specialist prescriptions, continued by the GP, and initial GP prescription.

Several measures have been taken by the Food and Drug Administration (FDA) for the improvement of the current "orphan status" of children regarding drug research. As part

of the FDA modernisation act, the "Pediatric Exclusivity Provision" was introduced to increase the numbers of paediatric registrations of drugs for children. Six extra months of patent exclusivity (the right to produce and sell a drug) could be obtained when drugs were issued for paediatric licensing. However, instead of intensified research on drugs most useful for the paediatric population, such as sympathicomimetics, and corticosteroids for respiratory use, many of the Written Requests that were issued for this 6-month exclusivity were cardiovascular drugs and other drugs that are rarely prescribed in the paediatric population but for which an extra 6 months of exclusivity is very lucrative in adults [28].

Although this study has been conducted in the Netherlands, where the healthcare system differs from many other European countries, results are relevant to Europe as well. Other studies have shown high frequency of unlicensed and off-label drug use for other European countries [29–32], and the labelling of drugs is equal or highly similar due to the increasing role of the European registration authority during the last decade. Most importantly, the conclusion that has to be drawn regarding the licensing of respiratory drugs in children concerns the Netherlands as well as all other countries.

Results show the high use of unlicensed and off-label use of respiratory drugs in children, while these are among the most commonly used drugs in children. The current shortage of formulations and dosage forms appropriate for infants and toddlers, especially, has to be resolved, and research on new and older drugs should include safety and efficacy studies in all appropriate paediatric age groups. Postmarketing surveillance of paediatric drug use should be intensified in order to increase the knowledge of safety and efficacy in a patient group, for which drug testing is restricted by ethical and practical boundaries.

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