

Unlicensed and Off-label Prescription of Systemic Anti-infective Agents to Children

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Background: Systemic anti-infective agents are frequently used for common paediatric diseases such as otitis media, upper and lower respiratory tract infections, rhinitis and sinusitis. We studied the use of systemic anti-infective agents by children to assess the extent of off-label and unlicensed use of anti-infective agents.

Methods: A population-based cohort study was conducted using the automated medical records in the Integrated Primary Care Information (IPCI) project in the Netherlands. The study population comprised a random sample (25%) of all children aged 0–16 years who were registered with a general practitioner during 1998. All prescriptions for systemic anti-infective agents during the study period were classified according to their licensing and off-label status.

Results: Within the study population of 13,426 children (51.7% male, median age 8.67 years), 2094 children received 2855 prescriptions for systemic anti-infective agents in 1998. 2425 (85.9%) prescriptions were licensed drugs. Of the remaining 430 prescriptions (15.1%), 20 (0.7%) were prescriptions for anti-infective agents unlicensed for use in children, and 410 (14.4%) were off-label prescriptions for anti-infective agents licensed to children. The one-year risk to receive an unlicensed or off-label anti-infective agent was 17% among children with at least one prescription for a systemic anti-infective agent.

Conclusion: This population-based study showed that a substantial proportion of systemic anti-infective agents prescribed by the general practitioner is licensed but prescribed in an off-label manner.

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Introduction

The extent and nature of unlicensed (UL) and off-label (OL) drug prescription in paediatric clinical care has been the subject of several surveys in Europe^{1–7}. 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').

Systemic anti-infective agents are used for several of the most common paediatric diseases such as otitis media, upper and lower respiratory tract infections, rhinitis and sinusitis; conditions that are treated in general practice rather than in hospital^{8–12}. Previous research by our group revealed that 51% of available systemic anti-infective agents in the Netherlands are not fully licensed for use in children, and many (64%) of these are registered only for specific age/weight groups¹³. We conducted a large cohort study in general practice to assess the extent and nature of unlicensed and off-label prescription of systemic anti-infective agents 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 of a group of 150 general practitioners (GPs) in the Netherlands. Within the Netherlands, patients are registered to a single general practitioner and records from each general practitioner can be assumed complete for an individual patient. The database is maintained by the department of Medical Informatics of the Erasmus Medical Center Rotterdam (EMCR), and contains coded and anonymous data on gender, age, symptoms, diagnoses and findings, and on prescriptions, their indications and dosage regimen. Summaries of hospital discharge letters and information from clinical specialists are included as free text. Patient complaints and diagnoses are entered as text and coded according to the International Classification for Primary Care (ICPC)¹⁴. Prescription drugs are

coded according to the Anatomical Therapeutic Chemical classification (ATC)¹⁵. The data are entered and stored directly by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who ensures anonymity of all information before further access is provided. To maximize completeness of information, GPs participating in the IPCI project are not allowed to use paper records. As of 2001, the IPCI database contains data on a cumulative number of 500,000 patients. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research¹⁶.

Design

We conducted a population-based cohort study 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 1998¹⁷. In 1998, 53,702 children were registered in the IPCI database. Since our research required manual review of all prescriptions we randomly sampled 25% of the population, which formed our primary study population. 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 years, transferring out of the practice, or end of the study period.

Classification of prescriptions

From the prescription file, we extracted all prescriptions plus their dosage regimens and indications issued to our primary study population in 1998. Systemic anti-infective agents were subdivided into "antibacterial drugs for systemic use" (ATC J01), "antimycotics for systemic use" (ATC J02), "antimycobacterial drugs" (ATC J04), "antiviral drugs for systemic use" (ATC J05), "sera and immunoglobulins" (ATC J06), and "vaccines" (ATC J07).

As part of a larger project¹⁷, all prescriptions for systemic anti-infective agents (ATC: J01, J02, J04–J07) were classified regarding their licensing

status³. The main, and mutually exclusive, classification categories were; “licensed for children”, “licensed, but used off-label” and “unlicensed for children” drugs. Prescriptions were classified as unlicensed drugs if they concerned: “new” drugs produced under a special manufacturing license; modifications to licensed drugs; drugs contraindicated for use in all children; and drugs for which no information was available on use in children. Prescriptions were classified as off-label if the drug was prescribed in a dose or dosage form other than that specified in the product license; by an alternative route; for an age below the age recommendations or for an indication not included in the license. Prescriptions could fit into more than one off-label subgroup. As a reference source for classification we used the official product license, as approved by the Dutch Medicines Evaluation Board. Age was classified in line with the paediatric age definitions provided by the U.S. Food and Drug Administration (FDA)¹⁸, but the categories “1 month – < 2 years” and “2 – < 12 years” were split because of heterogeneity within these age groups.¹⁹ Age groups used were: 0 – < 1 month; 1 – < 6 months; 6 months – < 2 years; 2 – < 6 years; 6 – < 12 years; 12 years and older.

Analysis

Descriptive analyses were conducted for patient demographics, prescription data and outcome. Statistical comparison consisted of independent two-sample *t*-tests for continuous variables, and χ^2 tests for discrete variables. 95% confidence

intervals were calculated around prevalence estimates based on the normal distribution.

Results

The primary study population comprised 13,426 children (51.7% male) with a median age of 8 years and 8 months on the last day of follow-up. A total of 18,399 pharmacological prescriptions were issued to the study population in 1998. 2855 prescriptions involving 48 different systemic anti-infective agents were issued to 2094 (15.6%) patients (Table 1). The mean age for systemic anti-infective agent users was significantly lower for anti-infective agent users than for non-users (6.8 years and 9.3 years, respectively; *P*<0.001). Children between the ages of 6 months and 2 years were the most likely to receive systemic anti-infective agents.

2774 (97.2%) prescriptions were for antibacterial drugs for systemic use (ATC J01). The most frequently prescribed drug classes were broad-spectrum penicillins (48.5% of all prescriptions), followed by macrolides (18.5%), broad-spectrum penicillin with a β -lactamase inhibitor (Augmentin®; 9.8%) and β -lactam sensitive penicillins (9.6%) (Table 2). Most frequently prescribed individual drugs were amoxicillin (48.4%), amoxicillin plus clavulanic acid (9.8%), azithromycin (7.8%), pheneticillin (7.3%) and clarithromycin (6.7%).

Of the 2855 prescriptions, 2425 (84.9%) were licensed for use in children, and prescribed in

Table 1. Characteristics of study population							
Age group	Children who used systemic anti-infective agents (n = 2094)		Prescription rate of systemic anti-infective agents per person year	Drug prescription-receiving children (n=6313) [†]		Total study population (n=13,426)	
	n	%		n	%	n	%
0 – < 1 month	2	<0.1	0.11	40	1	491	3
1 – < 6 months	61	2	0.22	342	5	952	6
6 – < 24 months	618	22	0.58	921	14	1,856	11
2 – < 6 years	1,091	38	0.37	1,797	27	3,855	23
6 – < 12 years	655	23	0.15	1,921	29	5274	32
12 years and older	428	15	0.13	1,562	24	4195	25
TOTAL	2,855	100		6,583	100	16,623	100

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 systemic anti-infective agents.

Table 2. Use of systemic anti-bacterial drugs and risk of unlicensed/off-label prescriptions

Drug class	Prescriptions				Patients		
	Total	Unlicensed	Off-label	%	Total	UL/OL [†]	%
Broad-spectrum penicillins	1,386	8	204	15	1,161	193	17
Macrolides	528	5	94	18	455	90	20
Broad-spectrum penicillins with enzyme inhibitors	281		27	10	239	24	10
Beta-lactamase sensitive penicillins	273		15	6	252	14	6
Tetracyclines	94		1	1	76	1	1
Sulphonamides with trimethoprim	77		25	33	58	19	33
Trimethoprim and derivatives	58		28	48	34	4	12
Beta-lactamase insensitive penicillins	36				33		
Cephalosporins and related compounds	31	1	1	3	26	2	8
Hydrazides	28		8	29	24	7	30

% Percentage within each drug class.

[†] Patients with an unlicensed or off-label prescription

Table 3. Most frequent off-label prescription of drugs

Drug	n	%	Off-label use
Amoxicillin	209	49	Dose
Azithromycin	68	16	Dose
Trimethoprim	28	7	Age/weight
Amoxicillin clavulanate	27	6	Dosage form
Sulphamethoxazole with trimethoprim	25	6	Dose
Erythromycin	16	4	Dose
Feneticillin	2	3	Dose
Roxitromycin	9	2	Age/weight
Amphotericin B	8	2	Dose
Clarithromycin	6	1	Age/weight
TOTAL	430	100	

concordance with the product license. Of the remaining 430 prescriptions, 20 (0.7%; 95%CI 0.5 – 1.1) were prescriptions for unlicensed drugs, and 410 (14.4%; 95%CI 13.1 – 15.7) were off-label prescriptions for licensed drugs. The most frequent off-label prescribed drugs were amoxicillin, azithromycin, trimethoprim, and amoxicillin clavulanate (Table 3). Modification of preparations (0.5%), and deviance of dosage recommendations (10.6%) were the most frequent reasons for unlicensed and off-label drug use, respectively (Table 4). The numbers of unlicensed and off-label prescriptions were highest in the age group “1 – 6 months” (23%; Table 5).

The one-year risk of an unlicensed or off-label prescription was 17% among children with at least one prescription for a systemic anti-infective agent. Unlicensed and off-label drug use differed for the various systemic anti-infective agent classes (Table 5). For children under 2 years of age, the risk of receiving unlicensed or off-label prescriptions was significantly higher than for older children; compared to 6 – 12 year olds, children in the age groups 1 – < 6 months, and 7 – < 24 months had a relative risk of 1.8 (95%CI 1.1 – 2.9) and 2.0 (95%CI 1.5 – 2.5) respectively. The risk of receiving an antifective agent off-label or unlicensed was highest among users of

Table 4. Off-label and licensing classification of systemic anti-infective agents			
Category	Subgroup	n=2855	%
Licensed in children		2,425	84.9
Off label	Age/weight	56	2.0
	Dose	296	10.4
	Dose & Frequency	11	0.4
	Dose & Indication	1	<0.1
	Dose & Dosage form	4	0.1
	Indication	9	0.3
	Dosage form	33	1.2
Total off-label		410	14.4
Unlicensed in children	Contra-indicated	6	0.2
	Modified preparation	14	0.5
Total unlicensed		20	0.7

Table 5. Number of drug prescriptions within licensing /off-label status			
Variable	Unlicensed / off-label		Licensed
	n	%	
Age Groups			
0 - < 1 month	0	0	2
1 - < 6 months	14	23	47
6 - < 24 months	132	21	484
2 - < 6 years	171	16	920
6 - < 12 years	84	13	571
12 years and older	27	6	401
Drug classes			
antibacterial drugs for systemic use	415	15	2,359
antimycotics for systemic use	8	27	22
antimycobacterial drugs	0	0	4
antiviral drugs for systemic use	4	100	0
sera and immunoglobulins	3	23	10
vaccines	0	18	30
Total	430	18	2,425

% Percentage within each age group / drug class

sulphonamides plus trimethoprim (32.8%) and macrolides (19.8%).

Discussion

This study showed a relatively low proportion of unlicensed and off-label use of systemic anti-infective agents (1% and 14%, respectively), when compared to all other drugs (18% and 14%, respectively)¹⁷. Although this is encouraging, it should be noted that many of the commonly used anti-infective agents have been available for decades, and are still not sufficiently labeled for

use in paediatric patients. Whereas age-restrictions are much more common for other drug classes like anti-asthmatics, the limited therapeutic range indicated in the dosage guidelines are frequently the reason for off-label prescription of systemic anti-infective agents. Not only may overdosing of systemic anti-infective agents be a potential threat to the health of the user, underdosing of these drugs may lead to development of resistance to the agent. Although formularies may provide prescribers updated dosage regimens^{20 21}, efficacy and safety data are not always provided, and dosage limits are often

based on experience, rather than evidence.

Evaluation of new and older systemic anti-infective agents in children is essential to provide appropriate paediatric dosing formulations. According to a Committee for Proprietary Medicinal Products (CPMP) guidance²², evaluation of new drugs in children should start as soon as sufficient data on safety have been obtained from pre-clinical studies and, except for agents aimed only at children, after preliminary evidence of safety and efficacy in adults. However, the International Conference on Harmonisation (ICH) draft *Note for guidance on clinical investigation of medicinal products in the pediatric populations* suggests it might not be necessary to perform clinical trials of efficacy in children for each indication, and the CPMP's *Points to consider on pharmacokinetic and pharmacodynamic (PK/PD) in the development of antibacterial medicinal products* mentions that detailed study of the PK/PD relationship for an antibacterial agent might potentially impact on the content of the clinical program in special populations. However, replacement of clinical trials with PK/PD relations of a drug to support the majority of indications is questionable, since knowledge of pharmacokinetics in children is still limited^{23, 24}.

Some information on the dosing scheme may be derived from pharmacokinetic population models that are built on retrospective data²⁵. Use of retrospective data for the development of accurate dosing regimens has potential benefits for the use of anti-infective agents. Since most of these drugs (especially the antibacterial agents) have been used over decades, much data is available for the development of pharmacokinetic models and optimisation of dosage regimens. Much effort should be taken to improve the quality of these forms of data gathering, and to improve the knowledge of pharmacokinetics in especially newborns and infants.

Paediatric labeling is necessary²⁶. It offers a clear and concise presentation of readily available and usable information approved by the European Medicines Evaluation Agency (EMA) as being substantial evidence of efficacy, safety and dose for the cited indications and age groups. However, for systemic anti-infective agents, and other drug classes, this is not the case.

In conclusion, this study showed that despite the long availability a considerable proportion of systemic anti-infective agents that are prescribed to children for common respiratory diseases in childhood in general practice are prescribed off-label.

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