Off label use of prescription medicines in children in outpatient setting in Estonia is common

Jana Lass¹,²*, Alar Irs³,⁵, Heti Pisarev⁴, Triin Leinemann⁵ and Irja Lutsar¹

¹Institute of Microbiology, Tartu University, Tartu, Estonia
²Pharmacy Department, Tartu University Clinics, Tartu, Estonia
³Division of Clinical Pharmacology, Tartu University, Tartu, Estonia
⁴Department of Public Health, Tartu University, Tartu, Estonia
⁵State Agency of Medicines, Tartu, Estonia

ABSTRACT

Purpose We aimed to analyse the availability of paediatric information in Summaries of Product Characteristics (SPC) of ambulatory prescription medicines used in children and to compare the SPC information with other information sources.

Methods In a cross-sectional drug utilisation study based on national prescription database, we analysed all dispensed prescriptions to subjects of <19 years in 2007. We reviewed SPCs of drugs for paediatric information and categorised them as being labelled, off-label and unlicensed.

Results Of 467 334 prescriptions dispensed to 151 476 children, 69% were for labelled, 31% for off-label and 0.05% for unlicensed drugs. The proportion of prescriptions for drugs being off-label because of missing data was the highest in genitourinary group (97%) and dermatologicals (74%); off-label use because of contraindication in the musculoskeletal group (69%). The highest proportion of off-label drugs was among children aged less than 2 years and the lowest for 2–6-year-olds. Contraindicated medicines were most often prescribed to adolescents. Systemic drugs were more frequently prescribed according to the label than topical agents. SPCs were found often not to be comparable with the other information sources.

Conclusions We show that one-third of Estonian children treated with prescription medicines are exposed to drugs not labelled for paediatric use. We believe that this is not only partly due to the limited number of paediatric trials but also due to lack of up-to-date information in the SPCs. We suggest that paediatric information should be regularly updated in SPCs to ensure that it is based on the best currently available evidence. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—children; paediatric drug information; off-label

Received 23 August 2010; Revised 1 February 2011; Accepted 4 February 2011

INTRODUCTION

The Summary of Product Characteristics (SPC) is intended to provide all necessary information for the drug to be used safely and effectively for its approved indications. However, because of the lack of evidence or regulatory delays in the SPC updates, paediatric recommendations are often missing.¹ Despite regulatory initiatives during the last decade intended to increase the availability of effective medicines for children,²,³ a lack of information on safety and efficacy of drugs for children still exists.⁴

Various definitions with different meanings have been used to describe the situation when drugs are not used according to the official drug information sources—e.g. off-label, off-license and unlicensed. The proportion of drugs prescribed outside the terms of product marketing authorisation has been studied intensively, and great variations between studies and countries have been described.⁵,⁶ It is likely that, at least, part of the variations between countries and studies are the result of the differences in the methodology and in the definitions used rather than of different medical practices.⁷ In Europe, most of these studies have been conducted in the 15 ‘old’ European Union (EU) member states. Data from the former Eastern bloc are very limited, and we are not
aware of any studies that systematically compared the paediatric information in SPC and other paediatric information sources.

We first aimed to describe the accordance of the ambulatory paediatric prescriptions to the SPCs. Second, we intended to analyse the availability of paediatric information in Estonian SPCs and to compare the information of most often used off-label drugs according to the SPC with other widely used drug information sources such as British National Formulary for children, (BNFC); Micromedex database, and Harriet Lane Handbook.\textsuperscript{8–10}

METHODS

Setting

Estonia is the smallest of the three Baltic States, which regained its independence from the Soviet Union in 1991. The country is situated on the eastern border of the EU and covers an area of 45 227 km\textsuperscript{2} being slightly larger than Denmark. As of 1 January 2007, the population of Estonia was 1 341 672 of which 277 265 (21\%) were children under 19 years old.\textsuperscript{11}

Estonian health care system is built around a compulsory, solidarity-based health insurance, and primary care is provided by family doctors. Access to health care is fully covered for all subjects aged below 19 years. Estonian Health Insurance Fund (EHIF) is responsible for purchasing care on behalf of the insured population including reimbursement of prescription medicines.

Design

A cross-sectional drug utilisation study was carried out based on the EHIF prescription database, which included data on all subjects aged below 19 years to whom a prescription medicine was dispensed during the period from 01 January 2007 to 31 December 2007. The database is comprised of pharmacy dispensing data, which are transferred electronically to the EHIF. The following data were extracted from the database: age and identification code of patient, the World Health Organization’s Anatomical Therapeutic Chemical (ATC) classification system code for the medicine,\textsuperscript{12} drug’s identification code, brand name and International Nonproprietary name, formulation, content per dose unit and number of packages dispensed.

The data were analysed in four age groups recommended by the guidelines of the International Conference of Harmonization (ICH-11) as follows: 0–23 months (infants and toddlers), 2–11 years (children) and 12–18 years (adolescents).\textsuperscript{13} The age group of 2–11 years was further divided into 2–5 (pre-school children) and 6–11 years old (schoolchildren), as this reflects more accurately a child’s ability to take solid drug formulations.

Data analysis

Descriptive statistics for prescription data were used, and the prescription rate (number of prescriptions per 1000 children) and crude 1-year prevalence of drug use in children (proportion of patients of the paediatric population who had one or more prescriptions issued) were calculated.

Assessment of licensing status of the drugs

The following four SPC sections of the medicinal products prescribed to children were reviewed by two authors (J. Lass, T. Leinemann) for paediatric information as of February 2009: indication (4.1), administration (4.2), contraindications (4.3) and warnings (4.4). Products with the same active substance but different brand name, dosage and formulation were evaluated separately, as they have separate SPCs.

Drugs were categorised according to the information in the SPCs into three—labelled, off-label and unlicensed as presented in Table 1. Off-label use was further divided into two groups—off-label because of lack of paediatric information and off-label because of contraindication.

A drug was considered off-label if it was prescribed to a child below the lowest approved age or outside of the age brackets mentioned in the SPC. There were four drugs (less than 0.3\% of all prescriptions) for which, for the consistency, the weight-based recommendations were transformed to the age-based. Enalapril, azitromycin and doxycyclin tablets were recommended for children over 15, 20, 45 and 50 kg, respectively. We transformed the weights to the matching age as follows: if the product was licensed for use over 15 kg, it got classified as to be licensed for children older than 5 years and over 20 kg, for those older than 12 years. If the product was labelled for children who are able to ingest solid dosage formulations or for school-aged children, we considered it to be licensed for children over 6 years old.

The availability of paediatric information in paediatric handbooks (BNFC and Micromedex database) was compared among 20 most often dispensed drugs that were off-label according to the SPC.

RESULTS

General pattern

A total of 467 334 prescriptions dispensed to 151 476 subjects aged below 19 years were identified within
the background population of 277,265, making the crude 1-year prevalence of 54.6%. GPs were responsible for 279,099 (59.7%) of the prescriptions, paediatricians for 72,213 (15.5%), the remaining 116,022 (24.8%) prescriptions came from specialists and others. The prescription rate was 1700/1000 children; those aged below 6 years received twice as many prescriptions (2500/1000 for those aged below 2 years and 2549/1000 for those aged 2–6 years) as children over 6 years old (1150/1000 for those aged 6–11 years and 1432/1000 for the adolescents). A total of 851 products with 309 unique active substances or combinations were prescribed.

Prescriptions

Altogether, 144,645 (31%) of prescriptions were off-label; the majority of those (n = 135,299; 29%) did not have any information of paediatric use in the SPC and 9346 (2%) were for drugs contraindicated for the respective age. There were 227 prescriptions (0.05%) for six products that had no marketing authorization in Estonia and were categorised as being unlicensed. Among different ATC groups, the percentage of off-label prescriptions due to lack of data in SPCs was the highest in genitourinary drugs group (97%), followed by dermatological (74%) and cardiovascular drugs (61%). The proportion of off-label prescriptions due to contraindication was the highest amongst musculoskeletal (69%) and nervous system (16%) drugs.

When the data were analysed according to the method of administration (Figure 1, panels a and b), it appeared that compared with topical drugs, a markedly larger proportion of systemic agents (more than 60% in all age categories and over 90% of prescriptions for the 2–5 years old) were labelled for children. The proportion of off-label topical drugs was the highest for those under 2 years old and for adolescents—only less than 40% of prescriptions had paediatric label (Figure 1, panel b).

During the study, we also found that about 2% of prescriptions given to children were contraindicated according to SPCs. Of 106 contraindicated products, 45 (42%) were contraindicated according to the SPC because of possible adverse drug reaction in children, 31 (29%) because there was not enough experience or no clinical trials conducted in children, in 23 (22%), the reason for contraindication was not specified; in six cases (6%), the dose of the product was too high for children and in one product, the excipients were not appropriate for children.

Products

The most commonly prescribed off-label products came from the frequently prescribed ATC groups, which are presented in Table 2—from respiratory system drugs and dermatologicals.

In all age groups, the proportion of off-label prescriptions was lower than for off-label products (Figure 1, panels c and d), a consequence of the lower prescription rate of the off-label products when compared to the drugs with adequate labelling.

Comparison of drug information sources

Notable differences were found when paediatric information in the SPCs of the frequently used off-label medicines was compared with other paediatric drug information sources; differences existed most often in nervous system medicines and anti-infectives (Table 3). The main discrepancy between the information sources was due to different age-related indications/contraindications.

Commonly used drug groups

‘Anti-infectives’ were by far the most commonly prescribed ATC group (Table 2) and with a few exceptions were generally labelled for use in children.
Amoxicillin/clavulanic acid tablets were extensively prescribed for all age groups and predominated among prescriptions for off-label drugs for those aged 6–18 years, as children are not mentioned in the SPC of Augmentin® tablets. Anti-infectives also had one of the biggest proportions of contraindicated prescriptions for adolescents because of the prescription rate of 11/1000 for quinolones.

The vast majority of ‘dermatological drugs’ were prescribed off-label mainly because of missing data in the SPCs. The most frequently prescribed off-label drugs for children under 12 years old were topical hydrocortisone and chlorhexidine combinations—prescription rates 207/1000, 60/1000 and 18/1000 for children <2, 2–6 and 6–11 years old, respectively. Topical anti-acne drugs aselainic acid (42/1000) and adapalene (35/1000) were the most commonly prescribed off-label drugs for adolescents.

Paediatric information for ‘respiratory system drugs’ was mostly lacking for those aged below 2 years—over half of the prescriptions were off-label because of the missing information (Table 2). Frequently prescribed off-label respiratory drugs for infants and toddlers were oral cetirizine drops (254/1000), followed by salbutamol syrup (156/1000) and for pre-school children, mometasone nasal spray (14/1000). Contraindicated respiratory system drugs were rarely used for older children, but the prescription rate in infants and toddlers was 24/1000 (mainly fusafungin spray). For pre-school children, contraindicated clemastine tablets (2/1000) were prescribed.

Among ‘drugs for sensory organs’, the prescribing of chloramphenicol ophthalmic drops accounted for most of the off-label drugs because of the missing data in the SPCs.

Over half of the prescriptions for ‘alimentary drugs’ had no information in the SPCs for children aged less than 12 years. The most common off-label drugs for infants and toddlers were multienzymes (12/1000) and for preschool and schoolchildren—drotaverine (spasmyloytic) tablets—prescription rates of 5/1000 and 9/1000, respectively.

Almost all ‘musculoskeletal drugs’ were contraindicated. Diclofenac suppositories were prescribed at a rate of 4/1000 for infants, the drug being indicated above the age of 1 year.

Prescriptions for drugs off-label because of lack of data counted for 98% of the prescriptions for ‘genito-urinary drugs’ in adolescents. There were over 20 000 prescriptions for hormonal contraceptives which have no information about use in the paediatric population. The most commonly prescribed contraindicated drugs for preschool children were ‘antiparasitic drugs’ (hydroxychloroquine, 3/1000) and for the school aged and adolescents, ‘nervous system drugs’ (tricyclic antidepressant nortriptylline, 2/1000 and selective serotonin receptor inhibitor escitalopram, 6/1000), respectively.

DISCUSSION

This study shows that in paediatric ambulatory setting in Estonia, one-third of the prescriptions are for off-label drugs mainly because of missing information in the SPCs. However, the data varies greatly depending
on the age, route of administration and ATC categories. Although almost half of the prescriptions for infants and adolescents are off-label, the proportions in preschool and schoolchildren are only approximately 10 and 20%, respectively. This is in accordance with the findings of a recent systematic review of hospital drug use showing that during inpatient stay, adolescents and infants receive off-label medicines most commonly. We also observed marked differences between the information provided in the SPCs (an official labelling source) and in widely used paediatric drug information sources such as BNFC and Thomson Micromedex database.

### Paediatric drug information

Compared to other studies using similar methodology (assessed off-label prescribing with regards to the age), the rate of off-label prescribing in Estonia (31%) was somewhat higher than in Sweden, the Netherlands and Germany. A Swedish study looking at the ambulatory prescriptions for children aged less than 16 years and using Swedish Physician’s Desk Reference found the off-label ambulatory prescriptions rate being 20.7%. Similar rates have been reported in the Netherlands based on the information in the SPC (20.6%). Bücheler et al. found that 13.2% of prescriptions for children in Germany were off-label, based on the information in SPC or drug lists provided by German pharmaceutical manufacturers’ associations (Gelbe Liste or Rote Liste). Whether these between-countries differences are real or are triggered by the differences in source documents could only be identified in international studies using the similar methodology and source documents in all countries.

We categorised our data based on the SPCs, as this is the only officially accepted and globally accessible source of information to prescribers. Manufacturers should keep SPCs up-to-date and be required to include all data from completed clinical trials. The information of the SPCs must also pass the control by local regulatory authorities. Despite that, significant differences in the content of the SPCs between countries have been observed, which explain partly the differences in off-label prescription rates in various studies. Surkenboom et al., when comparing the SPCs with that of the UK, Holland and Italy, reported that only 25% of the agents had the same age limit from which the drug was approved.

While reviewing SPCs, we noticed that even products with the same active ingredient and drug formulation, but produced by different companies had different paediatric information. For example, in the

### Table 2: Drug prescription rate (per 1000 children) in different age categories of children

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Total number of prescriptions</th>
<th>Off-label</th>
<th>Labelled</th>
<th>Off-label</th>
<th>Labelled</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1.99 years</td>
<td>1375</td>
<td>1090</td>
<td>35</td>
<td>2233</td>
<td>957</td>
</tr>
<tr>
<td>2–5.99 years</td>
<td>1156</td>
<td>1132</td>
<td>24</td>
<td>2233</td>
<td>957</td>
</tr>
<tr>
<td>6–11.99 years</td>
<td>140</td>
<td>138</td>
<td>2</td>
<td>1132</td>
<td>957</td>
</tr>
<tr>
<td>12–18.99 years</td>
<td>1350</td>
<td>1323</td>
<td>2</td>
<td>957</td>
<td>957</td>
</tr>
</tbody>
</table>

*CRI, contraindicated
SPC of cetirizine oral solution, for the brand name Aceterine® (Hexal AG, Holzkirchen, Germany), the SPC states that the product is contraindicated for children aged under 2 years; whereas the SPC of Zyrtec® (UCB Pharma Oy, Espoo, Finland) does not state such contraindication. The drug formulations, including excipients of these two products are exactly the same. It should be the role of the regulatory agencies to avoid this type of discrepancies in the SPCs. Confusion increases further when the SPC of cetirizine is compared with other paediatric information sources. According to the BNFC, cetirizine is not indicated for use in children aged less than 6 years except for 2–6 year-olds for the treatment of seasonal allergic rhinitis. According to the Thomson Micromedex, cetirizine is indicated for children aged over 6 months for the treatment of perennial allergic rhinitis and also chronic urticaria. The 16th edition of Harriet Lane Handbook recommends cetirizine for children aged over 2 years without mentioning specific indications or contraindications.

Table 3. Most commonly prescribed off-label drugs and the information in the Summaries of Product Characteristics (SPCs), British National Formulary (BNFC) and Micromedex

<table>
<thead>
<tr>
<th>Drug (ATC group)</th>
<th>SPC</th>
<th>BNF for children 2009</th>
<th>Micromedex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine oral drops (Zyrtec, Aceterin) (R)</td>
<td>Zyrtec: not recommended &lt;2 years; Aceterin: CRI</td>
<td>NL &lt; 6 years, doses for &gt;1 year</td>
<td>Doses for &gt;6 months</td>
</tr>
<tr>
<td>Salbutamol syrup (R)</td>
<td>Doses for &gt;2 years Not recommended &lt;2 months</td>
<td>NL &lt; 2 years, doses for &gt;1 month</td>
<td>L &gt;2 years</td>
</tr>
<tr>
<td>Amoxicillin + clavulanic acid granules for oral suspension (J)</td>
<td>Children mentioned only in warnings</td>
<td>L, doses for neonates and older</td>
<td>L &lt;3 months and older</td>
</tr>
<tr>
<td>Chloramphenicol eye drops (S)</td>
<td>Diclofenac suppositories (M) CRI, dose too high Children not mentioned</td>
<td>NL &lt;6 years</td>
<td>Safety &amp; efficacy not established, doses for neonates given</td>
</tr>
<tr>
<td>Fusidic acid cream (D)</td>
<td>Mometasone nasal spray (R) L&gt;6 years</td>
<td>L &gt;6 years</td>
<td>L &gt;2 years</td>
</tr>
<tr>
<td>Hydroxychloroquine tablet (P) CR1&lt;6 years</td>
<td>Metoclopramide tablet (A) CR1&lt;14 years</td>
<td>L &gt;1 month</td>
<td>L for malaria suppression</td>
</tr>
<tr>
<td>Amoxicillin + clavulanic acid tablet (J)</td>
<td>Children not mentioned L, starting from neonates</td>
<td></td>
<td>Safety and efficacy not established, doses starting from neonates</td>
</tr>
<tr>
<td>Clarithromycin tablet (J) Oral suspension is recommended for &lt;12 years</td>
<td>Nortriptyline tablet (N) CRI</td>
<td>L &gt;6 years</td>
<td>L adolescents</td>
</tr>
<tr>
<td>Escitalopram tablet (N) CRI</td>
<td>Sulphide tablet (N) CRI CR1 &lt;14 years</td>
<td>NL for depression; doses for obsessive-compulsive disorder &gt;6 years, doses for depression &gt;12 years</td>
<td>Safety and effectiveness not established; doses &gt;12 years</td>
</tr>
<tr>
<td>Sertraline tablet (N) CRI</td>
<td>Clindamycin topical solution (J) Children not mentioned L</td>
<td>For Tourette syndrome doses &gt;2 years</td>
<td>NA</td>
</tr>
<tr>
<td>Drosiprene+ ethinylestradiol tablet (G) Children not mentioned L</td>
<td>Ciprofloxacin tablet (J) CRI L &gt;5 years for pseudomonal infections in cystic fibrosis and for other children/other infections where benefit outweighs potential risks</td>
<td></td>
<td>Acne vulgaris: &gt;12 years</td>
</tr>
<tr>
<td>Dienogest+ ethinylestradiol tablet (G) Children not mentioned L</td>
<td></td>
<td></td>
<td>Contraception: after menarche, same dose as adults; Acne vulgaris &gt;14 years</td>
</tr>
<tr>
<td>Adapalene cream (D) Only information in SPC; not tested &lt;12 years</td>
<td>Ciprofloxacin tablet (J) CRI</td>
<td>L, dose starting from neonates</td>
<td>Safety and efficacy not established &lt;12 years; for acne vulgaris &gt;12 years</td>
</tr>
<tr>
<td>Ciprofloxacin tablet (J)</td>
<td></td>
<td></td>
<td>NL &lt;18 years except for treatment of anthrax and complicated urinary tract infections</td>
</tr>
</tbody>
</table>

CRI: contraindicated; L: labelled; NL: not licensed; NA: not included in the handbook or database.
Augmentin® (GlaxoSmithKline, Brentford, UK) tablets are most likely suitable for children aged above 6 years, but the SPC dosing recommendations for adolescents were given only for powder for oral suspension. There was no reference to paediatric use in the SPC of Augmentin® tablets, at the same time the SPC of Augmentin® suspension granules gives dosing information starting from 2 months of age. These results are even more intriguing because amoxicillin clavulanate has been extensively studied in paediatric population; the MEDLINE database search for the term ‘amoxicillin clavulanate’ identified 265 randomised controlled studies conducted in the age group of 0–18 years. We believe that the SPCs should be updated as the oral suspension may not be the best formulation for subjects who could otherwise swallow tablets. However, we accept that the prescription of amoxicillin clavulanate tablets to adolescents is off-label legally and not medically, provided that the bioequivalence between the tablets and the liquid formulation has been demonstrated.

We also observed some minor differences between the Thomson Micromedex and USFDA package insert at the USFDA website (drugs@FDA) for a few of the 20 most commonly prescribed off-label drugs (Table 3). These, however, did not change the classification of these drugs from off-label to the licensed category or vice versa.

In our study, similarly to Ufer et al., topical agents lacked paediatric recommendations in the SPCs more often than systemic drugs. The clinical relevance of this is still debatable. On the one hand, adverse drug reactions have been disproportionately more often reported on systemic than in topical drugs. On the other hand, not surprisingly, several cases of significant systemic absorption of topical and ophthalmic drugs leading to severe side effects have been observed. It is widely known that, with potentially toxic effects, the relative systemic exposure of topically applied drugs in children may exceed that of adults, thus demonstrating a need to increase the available amount of information about the use of topical drugs in children.

As off-label use of pharmaceuticals according to the SPC is and probably remains ubiquitous in the near future, and the authorities cannot provide evidence-based guidance for many medicines, practising clinicians have to continue to search drug information from other sources such as medical textbooks, scientific publications, case reports etc. As these sources are often scarce, have not undergone thorough regulatory review and often differ from each other, there is a risk of wrong dosing or unexpected safety events. This will continue to affect the selection of drugs and doses for children and will remain the source for discrepancies of medication use patterns as observed by investigators.

**Prioritisation of research in children**

We found that some extensively prescribed drugs with no paediatric data already appear in the European Medicines Agency priority list for children. At the same time, there are other frequently prescribed off-label drugs that are not included in the priority list, such as hormonal contraceptives in adolescents, cetirizine oral drops and salbutamol syrup in children aged less than 2 years.

We would like to emphasise that the missing information in the SPCs does not always mean that the scientific data is lacking and that there is a need for more studies. It has been suspected that the lack of information of paediatric use in the SPCs is partly the result of the over-cautious and delayed attitude of drug companies in formulating their SPCs.

**Limitations**

Some limitations of this study should be noted, which in our opinion do not affect the general reliability of the results. First, the diagnoses for which the drugs were prescribed were not recorded and thus prescriptions for different indications than contained in the SPC were not classified as off-label. Second, the study did not register over-the-counter drug use, but only prescription medicines—this could have an effect in the drug groups which are partly prescribed as over-the-counter medicines. Third, we only captured data collected within 1 year and thus were unable to analyse the trends in the drug use. However, the drug prescription pattern is found to be relatively stable, and even if changes occur, they are seen between specific drugs rather than between drug classes. Furthermore, the information in the SPCs is regularly updated, which could make the comparison of the off-label paediatric prescribing over time difficult.

**Conclusions**

We found that off-label use of prescription medicines in Estonian outpatient setting is common and that paediatric recommendations between SPCs and other paediatric drug information sources differ greatly. We consider that the latter is not only partly due to limited number of paediatric clinical trials but also due to reluctance and delay in introducing new information into the SPC. We suggest that in addition to conducting
a pan-European study with one methodology, the available information should be harmonised and regularly updated in SPCs to ensure that it is based on the best currently available evidence. The reasons for a drug not being recommended for paediatric use should be provided to inform the practitioners and to avoid ineffective and potentially dangerous use of medicines in children.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The study was supported by European Union through the European Regional Development Fund and by the Archimedes Foundation and Norwegian Financial Mechanism/EEA (grant EE0016), Estonian Science Foundation Grant No 6984 and Estonian Target Financing Grant No 2726.

KEY POINTS

• One-third of Estonian children treated with prescription medicines are exposed to drugs not labelled for paediatric use;
• Paediatric recommendations between SPCs and other paediatric drug information sources differ greatly;
• Compared with topical drugs, a markedly larger proportion of systemic agents are labelled for children.

REFERENCES


Copyright © 2011 John Wiley & Sons, Ltd.