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OFF-LABEL DRUG USE AMONG HOSPITALIZED CHILDREN: IDENTIFYING EXTENT AND NATURE

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Objective of the study was to determine the extent and nature of medicinal products used off-label in hospitalized children and to highlight the therapeutic areas with the highest need. Over a 4 week period, data about prescribed drugs to patients under 18 years of age at two paediatric wards in Bratislava (Unit for Infants and Unit for Older Children) were recorded and the drug-licensing status according to valid Summary of Product Characteristics (SPC) was identified. In total, 206 medicinal products containing 70 different generic substances were given to 49 paediatric patients at the Unit for Infants. Of these, 22% were evaluated as off-label. The highest rates were established among the drugs used for diseases of respiratory system and diseases of digestive system. The 68 children had been given at the Unit for Older Children 267 medicinal products resulting in 97 generic substances. In 15.7% of cases medicines were used in off-label manner, mainly due to unapproved paediatric indication and age. This pilot study provided a preliminary survey on drugs administered off-label to paediatric patients in Slovak Republic.

Keywords: *off-label prescribing – paediatrics – European legislation*

INTRODUCTION

Paediatric population accounts for approximately 25% of European Union's total population. Infants and children are considered to be particularly vulnerable to illnesses as well as to the potential harmful effects of medicinal products (Bush, 2006). Research and science in paediatric clinical pharmacology have achieved significant progress in the last decades. Despite evident progress, children and paediatricians have often limited or delayed access to modern drugs.Around 90% of patients in neonatal intensive care and almost 70% of children in general hospital

setting during a hospital stay in Europe received at least one medicine, which was either not labelled or inadequately labelled for use in paediatric patients (Tjong et al., 2001).
It is known as off-label use of medicinal products and it means that the product has not been clinically evaluated in particular age group, indication or in paediatric population at all (Pandolfini, 2005). A new legislation (Regulation EC No 1901/2006) entered into force in 2007 to improve the availability of safe and effective medicines for children in Europe. Accessibility of medicinal products developed with respect to paediatric needs should be facilitated according to the regulation (Medicines for children, www.ema.europa.eu, Regulation (EC) No 1901/2006 of the European Parliament and of the Council). For all mentioned purposes, an inventory of current prescribing patterns and of all paediatric uses of medicinal products in Europe was requested from EU Member States. There has not been any data submitted by Slovak Republic yet (EMA/794083/2009).

EXPERIMENTAL

The research was performed over a 4 week period during February and March 2011 in the Paediatric Unit for Infants and Children in University Children's Hospital (DFNsP) in Bratislava. The study included patients aged < 18hospitalised for at least 24 hours at one of the two mentioned units. Following data was collected from patient records:age, gender, weight, diagnosis, prescribed medication including the dose, dosing frequency, intended route of administration and formulation. The reasons for hospitalization and the indications were classified according to the International Classification of Diseases, version 10. Medicinal products were classified according to the World Health Organisation Anatomical Therapeutic Chemical Classification System (ATC). Intravenous replacement solutions, blood products, dietary supplements and topical medications were excluded. Each recorded medicine was reviewed for off-label use status, based on the information in the approved Summary of Product Characteristics. In particular, the information in sections 4.1, 4.2, 4.3 and 4.4, which refer to approved indications, posology, contraindications and warnings, was used. A dispensed medicinal product was regarded as off-label if it was given outside the terms of the drug labelling, based on approved indication and age range. Data was analysed using SPSS (version 16 for Windows).

RESULTS AND DISCUSSION

Together 49 patients from the Unit for Infants and 68 from the Unit for Older Children were involved in the study. Patients were either in hospital at the start of the study or were admitted over the 4 week study period.
The age of the infant subgroup ranged from 1 month to 6 years (mean = 1.5 years). The main reason for hospital admission, representing 2/3 of all diagnoses, were diseases of the respiratory system (47%); diseases of digestive system (14%); and symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified (12%).

Patients at the Unit for Infants received 206 medicinal products containing 70 different generic substances. According to the ATC classification the most commonly administered medicinal products, as presented in table 1, were drugs for diseases of the respiratory system (29%), anti-infectives for systemic use (21%), and drugs for the alimentary tract and metabolism (14%).
Of the total 206 analysed drugs administered to patients at the Unit for Infants, 44 (21%) were identified as off-label.

Table 1. Most frequently administered medicinal products according to the ATC classification system.

Group of drugs according to the ATC classification system	Percentages (%)
Drugs for diseases of the respiratory system	29
Anti-infectives for systemic use	21
Drugs for the alimentary tract and metabolism	14
Drugs for the musculo-skeletal system	9
Drugs for the nervous system	7
Drugs for blood and blood forming organs	6
Other	14

The off-label rates of the most common indications leading to prescription at the Unit for Infants during the study period are shown in figure 1. A third of all drugs administered for respiratory tract diseases were used in off-label manner, with regard to the age limits stated in SPC. Other area with a clinically important proportion of off-label drug use was found among medications prescribed for diseases of the digestive system. 32% of these drugs were classified as off-label in relation to the child`s age. Medicinal products most frequently used off-label due to age are demonstrated in table 2. Conroy et al. in United Kingdom and Dell´Aera et al. in Italy, both evaluating prescriptions at the neonatal intensive care unit, reported much higher incidence of off-label used drugs (54.7; 51%).

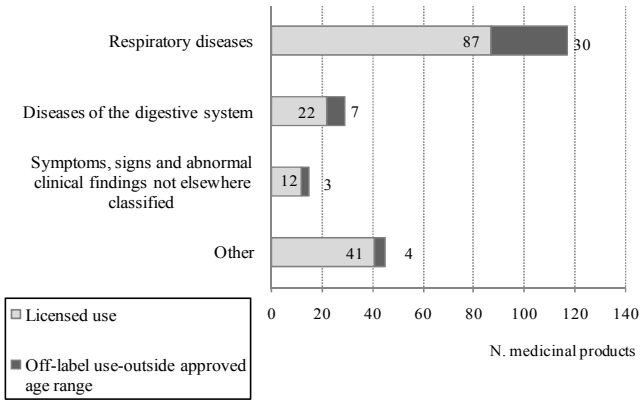

Figure 1. Distribution of most common diagnoses and administered drugs in Infants

In both surveys, the definition of off-label used medicinal products is comprised, apart from condition of use in not approved age range and indication, also of different dose and alternative route of administration according to the SPC. This fact could explain higher rates of off-label used drugs when compared to our results (Conroy et al., 1999, Dell`Aera, 2007).

Of the 68 patients at the General Unit for Older Children, 36 were male and 32 female. The age ranged from 2 to 18 years (mean = 10.4). Unlike the subgroup of infants, patients at this unit suffered mainly from diseases of the digestive system (29%), followed by diseases of the respiratory system (19%) (fig. 2). A total of 267 drugs resulting in 97 different generic substances were administered during the 4 week period. The number of prescriptions *per* patient ranged from 1 to 15 (mean = 4). Following drug groups according to the ATC classification were most frequently prescribed: J01 (16%), M01 (7%), R03 (7%), A11 (6%), A12 (5%). Of the 267 prescribed drugs 15.7% (42) were identified as off-label, 16 of which due to unapproved age range and the rest to unlicensed indications. In fact, the anti-infectives are the most commonly prescribed and at the same time, the most frequently used drugs in accordance with the terms of SPC. These findings clearly show that the off-label use of medicines occurs more frequently in newborns and infants than in older children. These results point out lower rates compared to those reported by other European studies, where the proportion of off-label use of medicinal products ranged from 18 to 62% (Khdour et al., 2011, [1]Pandolfini et al., 2002, Hsien et al., 2008, Conroy et al., 2000).

In general the difference can be explained by fewer off-label categories, especially concerning the dosage recommendation and suitable formulation. The study carried out by Lindell-Osuagwu et al. at three paediatric wards in Finland refers to 36% off-label drug use (Lindell-Osuagwu et al., 2009)

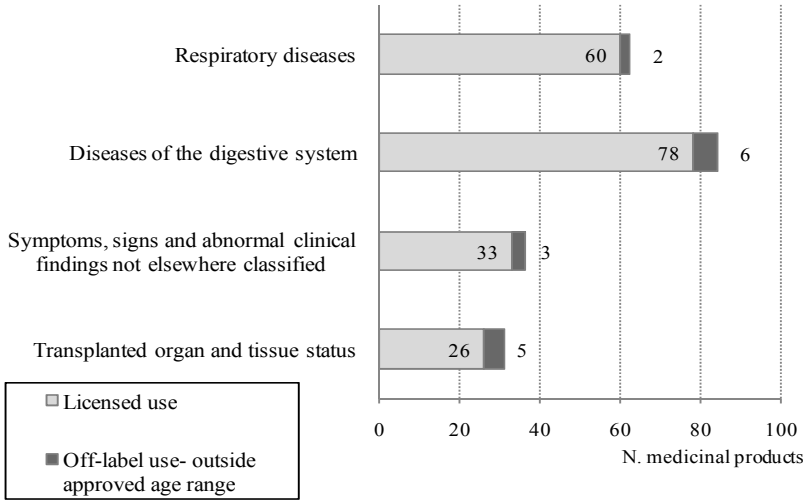

Figure 2. Distribution of most common diagnoses and prescribed medicinal products in older children.

The most frequent reason for off-label prescriptions was the absence of any direction for use in children, administration by an alternative route, deviation from the recommended dose followed by use in an inappropriate age range. The age group with the greatest off-label prescription rate was represented by children below 2 years. Interestingly, Conroy et al. identified administration of lower than recommended dose as the main reason for drug use being categorised as off-label (Conroy et al., 1999).

Table 2. Examples of off-label drug use in infants

Medicinal product	Active substance	ATC	N. of off-label (total)	Age limit for licensed use
Flixotide 50 Inhaler N	fluticasone propionate	R03	10 (14)	> 1 year
Atrovent N 20 µg	ipratropium bromide	R03	6 (7)	> 6 years
Ventolin syrup	salbutamol sulphate	R03	3 (3)	> 2 years

CONCLUSION

The present findings suggest widespread use of medicinal products in off-label manner in paediatric wards in Slovak Republic. This in-patient based study identified some important therapeutic areas, such as drugs for respiratory diseases (antiasthmatics) and medicinal products for alimentary tract and metabolism administered to infants aged less than 1 year. However, for the results to be generalized to the national level, more hospitals would need to participate. Limitations of the conducted survey are further related to the short study period and last, but not least, the small analysed sample. On the other hand, the essential goals of this pilot survey which included identification of the nature and extent of medicinal products used off-label in paediatric patients in Slovak Republic, were met. Proportion of off-label dispensing in the out-patient paediatric care would be interesting to research as well. Despite the aim of European initiatives to promote greater awareness and research in children, these outcomes demonstrate, that the rates of off-label and unlicensed drug use especially in neonatology remain high. More time is required for Paediatric regulation, the main legislation tool, to be reflected in more intensive development of medicines responding to children's needs. It is underlining the need to stimulate and motivate scientific data collection by means of specialised experimental studies and appropriate research in paediatric population.

REFERENCES

Bush A. Evidence-based medicines for children: important implications for new therapies at all ages. Eur Respir J. 2006;28:1069-1072.

Conroy S, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini CH, Raffaelli MP, Rocchi F, Bonati M, Jong G, Hoog M, Van Den Anker J.

Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ. 2000;320:79-81.

Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Fetal Neonatal Ed. 1999;80:F142-F145.

Dell`Aera M, Gasborro AR, Padovano M, Laforgia N, Capodiffiero D, Solarino B, Quaranta R, Dell`Erba AS. Unlicensed and off-label use of medicines at a neonatology clinic in Italy. Pharm World Sci. 2007;29:361-367.

Hsien L, Breddemann A, Frobel AK, Heusch A, Schmidt KG, Laer S. Off-label drug use among hospitalized children: identifying areas with highest need for research. Pharm World Sci. 2008;30:497-502.

Khdour MR, Hallak HO, Alaysa KSA, Aishahed QN, Hawwa AF, McElnay JC. Extent and nature of unlicensed and off-label medicine use in hospitalized children in Palestine. Int J Clin Pharm. 2011;33:650-655.

Lindell-Ouagwu L, Koronen MJ, Saano S, Hellin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther. 2009;34:277-287.

Medicines for children, European Medicines Agency. Available at:http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general_content_000302.jsp&mid=WC0b01ac058002d4ea (accessed on 10.07.2011).

Pandolfini C, Impicciatore P, Provasi D, Rocchi F, Campi R, Bonati M, The Italian Paediatric off-label collaborative group. Off-label use of drugs in Italy: a prospective, observational and multicentre study. Acta Paediatr. 2002;91:339-347.

Pandolfini Ch, Bonati M. A literature review on off-label drug use in children. Eur J Paediatr. 2005;164:552-558.

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union 49. Available at: http://eur-lex.europa.eu/(accessed on 20.07.2011).

Report on survey of all paediatric uses of medicinal products in Europe. EMA/794083/2009, 2011:1-37.

T Jong GW, Vulto AG, De Hoog M, Schimmel KJM, Tibboel D, Van Den Anker J. A survey of the use of off-label and unlicensed drugs in a Dutch children`s hospital. Paediatrics. 2001;108:1089-1093.

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OFF-LABEL POUŽITIE LIEKOV U HOSPITALIZOVANÝCH DETÍ: IDENTIFIKÁCIA ROZSAHU A CHARAKTERU

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Cieľom predloženej práce bolo stanoviť rozsah a charakter off-label použitých liekov u hospitalizovaných detí a súčasne zdôrazniť terapeutické oblasti s najväčším nedostatkom o vhodné lieky. Údaje o predpísaných liekoch pacientom do 18 rokov boli zbierané počas 4 týždňov na dvoch pediatrických oddeleniach Dojčenskom oddelení a Oddelení pre väčšie deti v Bratislave. Na základe informácií uvedených v platnom SPC bol identifikovaný status použitia každého lieku. Dojčenské oddelenie prijalo počas sledovaného obdobia 49 pacientov, ktorým bolo celkovo predpísaných 206 liekov obsahujúcich 70 liečiv. 22 % z celkového počtu podaných liekov bolo zaradených do skupiny off-label, pričom najvyšší podiel off-label použitých liekov sme zaznamenali pri liekoch určených na liečbu ochorení respiračného a tráviaceho traktu. Oddelenie pre väčšie deti prijalo počas trvania štúdie 68 detských pacientov, pričom predpísaných bolo 267 liekov, ktoré obsahovali 97 rozličných liečiv. Hlavným dôvodom pre off-label identifikáciu, ktorá na danom oddelení tvorila 15,7%, bolo použitie mimo schválenej indikácie a vekového limitu. Táto pilotná štúdia poskytla prvotné hodnotenie a prehľad o off-label predpisovaných liekoch hospitalizovaným pediatrickým pacientom v Slovenskej Republike.

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