



Exposure of Children in Serbia to Potentially Harmful Excipients When Treated with Approved Antibiotics

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SUMMARY

Introduction: According to current understanding of the role of excipient in medicines, they could not be considered as completely pharmacologically inert substances. Although excipients do not have the potential to cause adverse drug reactions (ADRs) in most patients, some of their negative effects have been established. Special caution regarding excipients intake is advised, especially in vulnerable populations such as pediatric one.

Aim: The aim of this paper was to investigate the exposure of children on antibiotic therapy to excipients with known effects (EKE).

Methods: During a one-month period antibiotic prescriptions data were taken from community pharmacies in Novi Sad, Serbia. Age, diagnosis and prescribed therapy were observed. Data about qualitative content of prescribed medicines were taken from Summaries of Product Characteristics (SmPC) available at the official website of Medicines and medical devices agency of Serbia (ALIMS). Excipients were considered to be potentially harmful if they were listed in European Medicines Agency (EMA) guidelines.

Results: The most commonly observed diagnosis was a respiratory infection, which affected more than 88% of children prescribed with an antibiotic. Only 5 out of 33 prescribed antibiotic formulations did not contain at least one EKE. Prescribed medicines mostly contained sodium compounds (77.78%), sucrose (34.07%) and sodium benzoate (31.11%). In addition, the following EKE were detected: propylene glycol, aspartame, sorbitol, lactose, potassium, mannitol, benzalkonium chloride, azorubine, parabens, sodium metabisulfite and sunset yellow. Around 75% of prescribed antibiotic formulations contained inappropriately labeled EKE (sodium and potassium compounds, sodium benzoate and propylene glycol). Additionally, inappropriately labeled information leaflets did not include possible adverse effects caused by the EKE.

Conclusions: This paper indicates high exposure of patients to EKE, where almost all children treated with antibiotics (96.3%) were simultaneously administered at least one EKE.

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We confirmed that approved medicines cannot meet the treatment needs of all patients, and that inappropriately labeled medicines carry a risk of ADRs, especially in newborns. Personalized treatment is especially important in children, as the appropriate dosage forms and diversity in formulation ingredients is lacking. Knowing the type and roles of each ingredient of the medicines it is possible to formulate a preparation that will meet all the individual children's needs.

Keywords: Drug Formulation, Excipients, Safety, Adverse Drug Reaction, Pediatrics

INTRODUCTION

Modern solid dosage forms contain one or more active pharmaceutical ingredients (API), and usually include additional compounds named excipients. There are various roles of excipients in these formulations, such as fillers, binders, disintegrating agents, lubricants, colour/taste altering agents, preservatives etc. Widespread basic requirements for considering a substance to be an excipient was physiological indifference in quantity taken in a single-dose while being physico-chemically compatible with other substances in the formulation. Understanding of the role of an excipient in medicines changed only until recently, in a way they could not be considered as completely pharmacologically inert substances.

Although excipients do not have the potential to cause adverse drug reactions (ADRs) in most patients, some of their negative effects have been demonstrated. Interaction with API is most commonly observed, but they can as well alter the pharmacokinetics or contain impurities [1]. Such excipients are called excipients with known effect (EKE) and their presence in medicines is not negligible [2]. Current legislative of the Republic of Serbia reflects on EKE in "Rulebook on the contents and method of labelling the outer and immediate packaging of a medicine, additional labeling, and contents of the package leaflet", published by the Ministry of Health and the Ministry of Agriculture, Commerce, Forestry and Water Management in 2010 [3]. Annex 1 of this Rulebook provides the list of EKE. Meanwhile, European Union assigned European Medicines Agency (EMA) for providing legislations regarding EKE. Most recent update from 2018 refers to Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. It includes profound list of EKE with information for the package

leaflet. Both documents require listing EKE contained in a medicine on the outer packaging of a medicine and in the package leaflet. That way EKE are seen as allowed medicine ingredients which require sufficient precaution [4].

Children are considered the most attention requiring subpopulation regarding medicine formulation, due to their capability to take a medicine, other illnesses or development stages [5]. Estimation of excipient toxicity depends on many factors, although it has not yet been widely understood. The majority of excipients contain a wide variety of chemical groups with possible chemical interactions, while the human organism shows high variability in metabolism, with pediatric population requiring special caution on ADRs [1,6,7].

AIM

The aim of this paper was to investigate the exposure of children on antibiotic therapy to EKE and to propose recommendations following principles of the era of personalized medicines.

METHODS

Antibiotic prescriptions data was collected from seven community pharmacies in Novi Sad, Serbia, part of the Health Institution „Cvejić" Pharmacy. Prescriptions were recorded during January 2018 in order to create non-commercial academic phase IV study of the data attained. This study exclusively took into consideration prescriptions funded by National Health Insurance Fund (NHIF). Specific data obtained were age, diagnosis and prescribed antibiotic therapy.

Data about qualitative content of prescribed medicines were taken from Summaries of Product Characteristics (SmPC) avail-

able at the official web-page of Medicines and Medical Devices Agency of Serbia (ALIMS) [8]. Excipients were considered to be potentially harmful if they were listed in guidelines given by European Medicines Agency (EMA) [4].

Continuous variables were presented as means with standard deviations, and categorical ones as frequencies in percentages. All data was analyzed and presented using Microsoft Office Excel (v16.0, 2019, Redmond, WA, USA).

RESULTS AND DISCUSSION

Observing the government funded prescriptions of antibiotics during one-month period in a chain of pharmacies, a total of 719 antibiotic prescriptions were recorded and analyzed. Out of whole, 18.78% (135 prescriptions) were intended for patients younger than 18 years, presented in this paper as pediatric population. The average recorded patient age was 8.01 ± 5.03 years. Following the Food and Drug Administration (FDA) Guidance (1998) [9], pediatric population was divided into following groups: neonates—younger than 2 months, making 1.54% of the specimen; infants — age from 2 months to 2 years old, 9.23%; developing children — from 2 to 12 years old, making 66.92%, and adolescents, 22.31% older than 12. Out of the total, 54.62% were girls and 45.38% boys.

Data presented in Figure 1. shows that the most common cause of antibiotic therapy were respiratory infections, where acute pharyngitis is taking first place with a share of 23.7%. It is followed by other respiratory infections up to a total share of 88.15%. Other causes were ear, eye and skin infections. Finally, urinary diseases and scarlet fever were

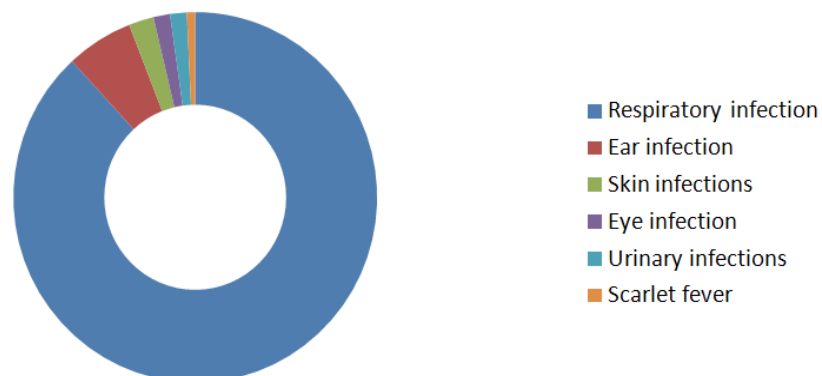
also observed in this study.

Analyzing prescribed medicines, it was visible that the biggest number of children were prescribed with macrolides (41.48%). Penicillin based medicines were prescribed in 32.59% of cases, followed by cephalosporins (20%). In total 33 different antibiotic formulations were prescribed and dispensed. All dispensed formulations were evaluated on the presence of the EKE according to EMA lists of potentially harmful excipients [4]. Excipients observed in this study were identified as EKE following this legislation and they are summarized in Table 1.

Additionally, individual formulations were presented in Table 2. According to EMA guidelines all potentially harmful excipients should be listed in Section 2 of SmPC. If an ingredient of a formulation is listed in EMA guidelines, but has not been declared in Section 2 of SmPC, that EKE was marked as inappropriately labeled. ADRs of EKE which were appropriately labeled were clearly stated in all examined SmPCs. Meanwhile, ADRs of inappropriately labeled EKE were not declared. Furthermore, referring to common side effects such as stomach distress or allergic reactions, it was impossible to make a difference between ADRs of an API in the SmPC.

At the moment of this study, the latest regulation regarding EKE in the Republic of Serbia dates from 2010, while European Union legislative has been regularly updated. Both regulations provided following information: EKE name, threshold, warning statements (obligatory on the package leaflet) and comments for the expert readers. Besides, EU legislative also provides date of the last update and regularly includes new EKE to the list. Information regarding identified EKE were compared between two documents and will be

Figure 1. Shares of different diagnosis observed in the specimen.



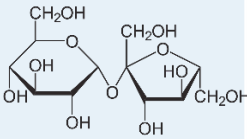
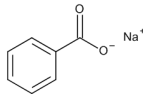
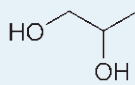
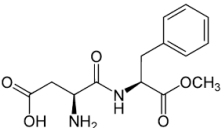
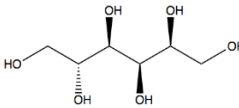
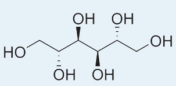
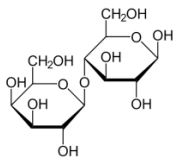
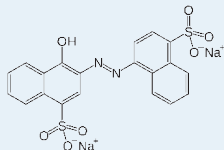
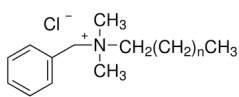
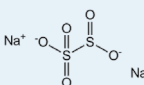
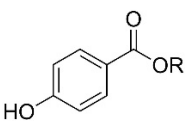
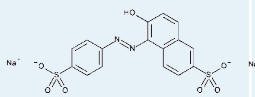
Excipient	Structural Formula	Functional Category and Common Concentrations [9]	EMA Comments [4]	Prescription Share (%)	Age Groups Prescribed with EKE
Literature Data			Observed Data		
Sodium	Na ⁺	As sodium chloride: -Diluent (tablets and capsules); 10-80% -Lubricant, channeling agent, osmotic agent (tablets and capsules); 5-20% -Tonicity agent (liquid formulations); ≤0.9%	"It is especially relevant to products used in children or in patients on a low sodium diet"	77.78	Infants, developing children, adolescents
Sucrose		-Sweetener/preservative (oral liquid formulations); 67% -Binder (tablets, dry granulation); 2-20% -Binder (tablets, wet granulation); 50-67% -Coating agent (tablets); 50-67%	"Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine."	34.07	Infants, developing children, adolescents
Sodium benzoate		-Antimicrobial preservative; 0.02-0.5% -Lubricant (tablets and capsules); 2-5%	"Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus"	31.11	Infants, developing children, adolescents
Propylene glycol		-Antimicrobial preservative; 15-30% -Humectant; 15% -Solvent or co-solvent (oral liquid formulations); 10-25%	"Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects"	20.74	Infants, developing children, adolescents
Aspartame		Sweetening agent; n.d.	"Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria"	19.25	Infants, developing children, adolescents
Potassium	K ⁺	As potassium sorbate: -Antimicrobial preservative; 0.1-0.2%	"It is especially relevant to products used in pediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K ⁺ in the product."	11.85	Infants, developing children, adolescents

Table 1. Summary of know traits of observed EKE in antibiotic formulations and overall exposure [4,10].

n.d. - non defined

Excipient	Structural Formula	Functional Category and Common Concentrations [9]	EMA Comments [4]	Prescription Share (%)	Age Groups Prescribed with EKE
Literature Data			Observed Data		
Sorbitol		-Humectant; 3-15% -Plasticizer; 5-20% -Binder and filler (tablets); 25-90%	"Patients with hereditary fructose intolerance must not be given this medicine unless strictly necessary."	16.30	Infants, developing children, adolescents
Mannitol		-Diluent (tablets and capsules); 10-90% -Sweetening agent; n.d	"May have a mild laxative effect."	4.44	Developing children, adolescents
Lactose		-Binder (tablets); n.d. -Filler (tablets and capsules); n.d. -Diluent (tablets and capsules); n.d.	"Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine."	20.74	Neonates, developing children, adolescents
E122 (azorubine)		Coloring agent; n.d.	"May cause allergic reactions."	2.22	Developing children
Benzalkonium chloride		Antimicrobial preservative; 0.01-0.02%	"Benzalkonium chloride may cause eye irritation"	4.44	Infants, developing children, adolescents
Sodium metabisulfite		Antioxidant, 0.01-1%	"May rarely cause severe hypersensitivity reactions and bronchospasm."	1.48	Developing children
Parabens		Antimicrobial preservative; 0.18% (methylparaben)+0.02% (propylparaben)	"May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm."	0.74	Developing children
E110 (Sunset Yellow)		Coloring agent; n.d.	"May cause allergic reactions."	0.74	Developing children, adolescents

discussed individually.

In the data obtained through this research, most commonly observed EKE was sodium ion, detected in various salts. Although its' intake through food is more dominant, the amount of sodium administered as excipients in drugs should not be neglected. In the litera-

ture, other than renal illness or hypertension in children, where medical practitioners are well aware of special caution regarding sodium intake [11,12], some studies have questioned the influence of sodium exposure in children on future hypertension [13]. The sodium intake through medicines has been discussed

Active compound	Formulation	Formulation Type	Prescription Share (%)	Observed EKE	Inappropriately
Amoxicillin	1	Orodispersible tablet	3.70	Aspartame, mannitol, sodium	Sodium
	2	Powder for oral suspension	8.89	Sodium benzoate, aspartame, sodium	Sodium
	3		4.44	Sodium benzoate, sodium, sucrose	Sodium benzoate, sodium
Amoxicillin/ clavulanic acid	1	Film tablet	2.96	Sodium	Sodium
	2		1.48	Sodium	Sodium
	3		0.74	Sodium, propylene glycol	Sodium, propylene glycol
	4		0.74	Sodium, propylene glycol	Sodium, propylene glycol
	5	Powder for oral suspension	0.74	Sodium, propylene glycol	Sodium, propylene glycol
	6		0.74	Sodium, mannitol	Sodium
	7		2.22	Aspartame	-
	8		1.48	Propylene glycol	Propylene glycol
	9		1.48	Propylene glycol	Propylene glycol
	10		2.96	-	-
Cefalexin	1	Hard capsule	0.74	-	-
	2	Powder for oral suspension	1.48	Sodium benzoate, sucrose	Sodium benzoate
	3		2.22	Sucrose, sodium benzoate, sodium, E122 (azorubine)	Sodium benzoate, sodium
Cefadroxil	1	Powder for oral suspension	0.74	Sucrose, sodium benzoate, sodium	Sodium benzoate, sodium
Cefprozil	1	Powder for oral suspension	0.74	Aspartame, E110 (Sunset Yellow), sodium benzoate, sodium chloride, sucrose	Sodium benzoate, sodium chloride
Cefixime	1	Film tablet	1.48	-	-
	2	Powder for oral suspension	7.41	Sucrose, sodium benzoate	Sodium benzoate
	3		1.48	Sucrose, sodium benzoate	Sodium benzoate
Cefpodoxime	1	Powder for oral suspension	3.70	Sodium benzoate, aspartame, sucrose	Sodium benzoate
Azithromycin	1	Film tablet	2.22	Sodium	Sodium
	2	Hard capsule	8.15	Anhydrous lactose	-
	3	Powder for oral suspension	4.44	Sodium, sorbitol, propylene glycol	Sodium, propylene glycol
	4		11.11	Sodium, sorbitol, propylene glycol	Sodium, propylene glycol
Clarithromycin	1	Film tablet	3.70	Sodium, lactose monohydrate	-
	2	Powder for oral suspension	11.85	Sucrose, potassium	Potassium
Doxycycline	1	Hard capsule	0.74	Lactose monohydrate	-

Table 2. Analysis of the presence of excipients that can cause ADRs in examined antibiotic formulations.

Active compound	Formulation	Formulation Type	Prescription Share (%)	Observed EKE	Inappropriately
Trimethoprim/ sulfamethoxazole	1	Oral suspension	0.74	Methylparaben, propylparaben, sorbitol	-
Neomycin/ dexamethasone	1	Drops	2.22	Sodium, benzal- konium chloride	Sodium
	2		1.48	Sodium, benzal- konium chloride, sodium metabi- sulfite	Sodium
Gentamycin	1	Drops	0.74	Sodium, benzal- konium chloride	Sodium

risk in children, but confirmed the fear of perceiving sodium as harmless excipient.

Second most commonly observed EKE was sucrose. It is still profoundly used as an excipient, while the number of young patients with metabolic syndrome is increasing [16]. Similarly, concerns about the correlation with dental caries prevalence in children also exist [17], which requires attention regarding intake of liquid formulations containing high concentrations of sucrose. Both EMA and Serbian regulations require declaration of content above 5 g of sucrose and special caution in children with diabetes mellitus. All formulations in this study adequately labeled sucrose and stated necessary precautions.

Nevertheless, when it comes to frequency, every third formulation in this study contained sucrose. Although the significance of compliance due to taste cannot be neglected, it brings to question why this excipient was not more commonly replaced with artificial sweeteners. Several antibiotics such as cephalexin and cefixime, contained sucrose in every medicine formulated as oral suspension in this study. However, there are compounding powders for oral suspensions of cefalexin or cefixime without sucrose intended for children with diabetes.

Sodium benzoate use in neonates should be strictly avoided, due to increasing neonatal jaundice [18]. EMA legislative requires declaring the content of sodium benzoate on the package leaflet, which is not required by Serbian legislative. Additionally, Serbian regulations recognize sodium benzoate as EKE only in formulations for parenteral and topical application, not in oral dosage forms. As a result, only one of the examined formulations had labeled sodium benzoate appropriately, but neither one of them stated the quantitative content of this EKE. Having in

mind that (i) 31.11% of prescribed medicines in this study contained this EKE, (ii) most of the formulations have not been appropriately labeled, and (iii) all formulations containing sodium benzoate were powders for oral suspension, making the risk of accidental intake in neonates rather high.

Similarly, propylene glycol has also been prohibited in children under 1 month old, due to the risk of hyperosmolarity, lactic acidosis and renal/hepatic toxicity [19–21]. It has been shown that propylene glycol had three times longer half-life in neonates than in adults [5]. EMA is strict regarding the intake of propylene glycol in neonates, children under the age of 5 years, and those with kidney/liver damage, where the declaration of quantitative content is necessary. These requirements are not present in the Serbian legislative, while the threshold for labeling as EKE is significantly higher. In this study that included infants, developing children and adolescents, every fifth child was given a medication containing propylene glycol. Neither of the formulations containing propylene glycol stated the EKE appropriately. This might be due to a threshold of 200mg/kg, which is significantly higher than EMA regulations. According to EMA, all formulations containing more than 1mg/kg/day of propylene glycol should declare the quantitative content of EKE: Furthermore, EMA suggests that children under 5 should not be given medicine that contains more than 50 mg/kg/day of propylene glycol. As no information regarding the content of propylene glycol was contained in SmPC, health professionals cannot make appropriate decisions when choosing the right formulation or analyze the origins of acute side effects.

Although no neonates were prescribed with neither sodium benzoate nor propylene glycol, precaution is necessary. Two

EKE were observed in 70% of formulations of powders for oral suspension within this research. Only a few formulations, containing amoxicillin/clavulanic acid and trimethoprim/sulfamethoxazole as API, contained other excipients, which significantly reduces the choice of antibiotic therapy in sensitive populations. This constraint can easily be addressed by compounded medicines, where ingredients could be adjusted to patients' needs.

Artificial sweeteners, such as aspartame, are declared safe for children of all ages [22]. Nevertheless, assessments are still conducted due to a lack of studies in human subjects, having neither non-clinical nor clinical data to assess aspartame use in infants below 12 weeks of age [4,23]. The main precaution regarding aspartame intake refers to patients with phenylketonuria, as aspartame is a known precursor of phenylalanine [22]. Although the prevalence is somewhat low in the general population, the ADRs could be severe and appropriate labeling is necessary. At the moment of this research, EMA requires a declaration of quantitative content in information leaflet, which is not required by authorities in Serbia. All formulations containing aspartame appropriately stated this EKE and possible side effects in the SmPC, but the quantitative content was not stated. Pediatrician decision between intake of natural and artificial sweeteners through medicines must be driven by individual patients' needs and perhaps appropriate notations would improve the process.

Other carbohydrates EKE identified in this research—sorbitol, lactose, and mannitol, have similar metabolism pathways. These excipients are contraindicated in patients with different sugar hypersensitivity, while mostly cause stomach distress or laxative effect due to osmotic properties [24]. Common is intolerance to lactose, where pediatricians should be well aware of dosage form ingredients when choosing the right medicine [25]. It is important to note that children below the age of 2 who may not yet be diagnosed with hereditary fructose intolerance [4], which could lead to toxicity of sorbitol as a source of fructose.

Serbian requirements for lactose and mannitol are harmonized with EMA, while for sorbitol EMA additionally requests stating the quantitative content. Sorbitol and lactose were appropriately labeled in SmPC, while mannitol was not noted in Section 2 of SmPC in either of the formulations that contained it. This

might be explained due to the high threshold in both EMA and Serbian legislative, which is 10g for mannitol. It leads to the conclusion that the total amount of EKE was less than 10g and that those formulations were appropriately labeled.

Effervescent formulations [5] usually contain large amounts of potassium salts, which requires attention for patients with reduced kidney function. In this research potassium was observed in one formulation in form of potassium sorbate. Both EMA and Serbian regulations require stating quantitative content of potassium in the information leaflet, regardless of the amount. The formulation with detected EKE did not provide appropriate labeling. Although no larger concentrations of this excipient are expected in powder for oral suspension, the necessity of consistency in labeling is important especially in reassuring parents on low potassium content in a medicine [4].

Antimicrobial drops prescribed to pediatric patients in this study, both contained benzalkonium chloride. This preservative has a known effect of mucosal irritation [26], which could significantly decrease compliance to the prescribed medicine in children [4]. While current EU regulations require stating the content of benzalkonium chloride on the package leaflet, this information is not required for approved medicines in the Republic of Serbia. Nevertheless, the formal requirement was satisfied and this excipient was appropriately labeled as EKE.

Another antimicrobial agent, paraben mixture (propyl and methyl parabens) is as well under the public eye as endocrine disruptors and allergen, where its influence on health is continuously examined [27,28]. EMA and Serbian regulations require appropriate labeling of these EKE as well as stating possible ADRs, which was satisfied in examined formulation SmPC. Both benzalkonium chloride and parabens carry actual risk in children and these formulations could easily be replaced with compounded ones.

Similarly, azorubine and sunset yellow, both azo dyes used in food and medicine, have been observed to cause allergic reaction in children [29]. Recent research are done regarding carcinogenic effects of azo dyes, with many forms of aromatic amines being the products of their metabolism [30]. Medicines containing these dyes were appropriately la-

beled. These dyes were found in only two out of ten cephalosporin formulations examined in this study and pediatricians were able to choose the appropriate formulation.

Sodium metabisulfite is registered in one formulation as antioxidant. Although it is thought to be generally safe, the sensitivity to this EKE is noted in 3-10% of asthmatic children [31]. EMA and Serbian regulative request declaring the EKE name in the information leaflet with the comment regarding possible hypersensitivity, which was found to be appropriately labeled. Thus health providers are adequately informed before making a decision between different formulations containing same EKE and recognizing ADRs.

Macrogol and sodium lauryl sulfate are two commonly used lubricants in solid dosage forms, which can have a laxative effect in children [32]. On the other hand, the off-label topical use of oral antibiotic formulations requires caution regarding skin irritation [33]. In this study, it was observed that 15.55% of patients were exposed to formulations containing macrogol and 10.37% to those containing sodium lauryl sulfate, while it is important to mention that one formulation contained both EKE: As these excipients were not recognized by the guidelines of the Republic of Serbia, there was no need to highlight their content in any of the approved antibiotics in this study. This requires considerable attention from decision makers, as the possibility of macrogol side effects is well known [34]. If appropriate information has been provided, patients with a history of allergic reactions or acute intestinal distress should be given another formulation that does not contain these excipients. Lastly, the off-label use of formulations containing sodium lauryl sulfate for topical use may cause adverse reactions. The same side effect was observed with off-label use of propylene glycol [5]. Healthcare professionals should carefully evaluate the content of the formulation before making a decision on off-label prescribing. A lower risk of side effects can be expected in the case where the antibiotic formulation for topical use is made from pure active substances and not by crushing the finished pharmaceutical forms.

Overall this study demonstrated that EKE are widely present in registered pediatric antibiotic formulations in the Republic of Serbia. Data represented in Table 1. has shown us several antibiotic formulations can

be found containing different excipients, while most obvious problem is seen with antibiotic eye drops, containing identical EKE. Lack of choice encountered by pediatricians when addressing specific needs of a patient should be avoided. In the age of ever-growing antimicrobial resistance, pediatric patients should not be kept away from the effective medicine due to adverse reaction to EKE.

Numerous studies have shown the essential need of dose adjustments for newborns as well as for older children with specific therapy needs [35,36]. Some hospital practitioners in developed countries advocate adjustment of the commercial dosage forms to requirements of all pediatric subgroups [37]. Serbia, as a developing country with a small market, may not find this model suitable, while process of compounding reemerges as more appropriate way to address specific needs of an individual patient [38]. Knowing so, hospital and community pharmacists could follow the example of many developed countries and rebuild their trust in medicines compounding as a direction towards personalized medications.

CONCLUSION

This study has shown us that EKE are widely present in pediatric formulations. Although they are considered to be safe, they may significantly deteriorate patients' wellbeing. The effect of excipients due to the immaturity of metabolic pathways, allergic reactions, intolerance, lack of specific enzymes, etc., rarely occurs but may have serious consequences. Known potentially harmful excipients, such as sodium compounds, sucrose, sodium benzoate and others are still profoundly used.

Several formulations prescribed in this study contained inappropriately labeled EKE thus misinforming the health providers. Furthermore, comparing official legislation regarding EKE in the Republic of Serbia to EMA legislation, the necessity for legislative update has been observed.

Personalization of therapy is especially important in children, where appropriate dosage forms and diversity in formulation ingredients are lacking. Knowing the role of each ingredient of the medicine it is possible to formulate a drug that will be able to address all individual needs of a patient. The necessity for reviving medicines compounding in pharmacies is reemerging as a faster, cheaper and fair

way to accomplish personalization of therapy.

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CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Izloženost dece u Srbiji lečene odobrenim antibioticima potencijalno opasnim ekscipijensima

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KRATAK SADRŽAJ

Uvod: Prema trenutnom shvatanju uloge ekscipijensa oni ne mogu biti posmatrani kao isključivo farmakološki inertne supstance. Iako ekscipijensi sa poznatim efektom neće izazvati neželjene reakcije kod većine pacijenata, neki od neželjenih efekata su dobro poznati. Poseban oprez prema njihovom unosu je neophodan, pogotovo u osetljivom uzrastu kakav je dečiji.

Cilj: Cilj ovog rada je istraživanje izloženosti dece na antibiotskoj terapiji ekscipijensima sa poznatim efektom.

Metodologija: Prikupljeni su podaci o propisanim antibioticima namenjenim deci u periodu od jednog meseca u lancu apoteka u Novom Sadu. Posmatrani su uzrast, dijagnoza i propisana terapija. Kvalitativni sadržaj propisanih formulacija bio je dostupan na veb-sajtu Agencije za lekove i medicinska sredstva, a ekscipijensi su identifikovani kao potencijalno opasni prema smernicama Evropske agencije za lekove.

Rezultati: Respiratorne infekcije su bile najčešći razlog za propisivanje antibiotika u ovom ispitivanju, u čak 88% dece. Od ukupno 33 propisane antibiotske formulacije, samo pet nisu sadržale ni jedan ekscipijens sa poznatim efektom. Najčešće sadržani ekscipijensi bili su soli natrijuma (77,78%), saharoza (34,07%) i natrijum benzoate (31,11%). Takođe su uočeni i propilen glikol, aspartam, sorbitol, laktoza, kalijum, manitol, benzalkonijum hlorid, parabeni, natrijum metabisulfit i boje. Oko 75% prepisanih antibiotskih formulacija sadržavali su ekscipijense (natrijum, kalijum, natrijum benzoat, propilen glikol) koje su bili nepravilno označeni. Dodatno, neadekvatno označene formulacije nisu sadržavale opisana neželjena dejstva uzrokovana od strane tih ekscipijensa.

Zaključak: Ovo istraživanje je ukazalo na visoku izloženost pacijenata potencijalno opasnim ekscipijensima, gde je većina dece (96,3%) dat makar jedan takav ekscipijens. Potvrdili smo da odobreni antibiotici ne mogu da budu pogodni za sve pacijente i da neadekvatno obeležene formulacije predstavljaju rizik za nastanak neželjenih dejstava, pogotovo kod novorođenčadi. Personalizovana terapija je posebno značajna kod dece s obzirom na nedostatak odgovarajućih doziranih oblika i raznolikosti sastojaka u formulacijama. Poznavajući vrstu i uloge svih sastojaka lekova, moguće je formulisati preparate koji će moći da zadovolje individualne potrebe svakog deteta.

Gljučne reči: formulacije lekova, ekscipijensi, bezbednost, neželjene reakcije, pedijatrija

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