A retrospective and observational analysis of harmful excipients in medicines for hospitalised neonates in Latvia

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ABSTRACT

Background Medicines used in neonates contain different excipients, which may not be safe in this age group.

Objective To analyse the frequency at which hospitalised neonates are exposed to harmful excipients (HEs) and to identify substitution possibilities for medicines containing HEs.

Materials and methods Retrospective, observational study at a university paediatric hospital from 1 September 2015 till 29 February 2016. All hospitalised neonates who received a prescription for medicines containing an HE were included. Neonates were divided into four groups according to gestational age (<28 weeks; 28 to <32 weeks; 32 to <37 weeks and ≥37 weeks). The following excipients were analysed: parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol, ethanol and benzalkonium chloride. Excipients were identified from the Summaries of Product Characteristics.

Results 296 (102(34.5%) preterm) neonates included in the study received 1472 prescriptions for 106 medicines. The most often used formulations were intravenous (48/106; 45.3%) and oral solid formulations (20; 18.9%). The total number of different excipients was 169. In total, 29/106 (27.4%) medicines contained at least one HE. In total 82/102 (80.4%) preterm and 118/194 (60.8%) term neonates received medications with at least one HE. Substitution was possible for 9/29 (31.0%) HE-containing medicines.

Conclusions Use of HEs can be reduced by using HE-free products available on the European market. However, medicine substitution was possible in only a small number of cases. Therefore the main focus should be on information and education of the hospital specialists about HEs used in medicines and their adverse reactions.

INTRODUCTION

Despite widespread use of different excipients in medicines for neonates, there is a lack of detailed description of the extent of such use in neonatal medicines. The pharmacokinetics and safety of many of these agents (eg, ethanol, benzoates) are still not well described.^{1,2} Although excipients should have limited pharmacological activity, there are an increasing number of adverse reports in paediatric populations.^{3,4} This is mainly because pharmacokinetics and pharmacodynamics of excipients in neonates may have different activity than that in adults and therefore might create adverse reactions.^{5–7} For instance, benzyl alcohol may have a

Key messages

What is already known on this subject

- ▶ Generally, pharmaceutical excipients have been considered to be pharmacologically inactive and safe.
- ▶ Some pharmaceutical excipients have been associated with toxicity in neonates.
- ▶ The extent of excipient use in neonatal medicines is still poorly studied.

What this study adds

- ▶ Hospitalised neonates in Latvia receive medicines containing harmful excipients (HEs).
- ▶ The medicines' substitution was possible in only a small number of cases.
- ▶ Collaboration between stakeholders at the local and European level is required to solve the different problems associated with substitution.
- ▶ The main focus should be on information and education of hospital specialists about HEs and their possible adverse reactions.

fatal toxic syndrome in premature infants.⁸ It 'must not be given to premature babies or neonates' and it 'may cause toxic reactions and allergic reactions in infants and children up to 3 years old'.⁹ Probably one of the best known cases in this regard is the so-called E-ferol incident. Thirty-eight premature low birth weight (<1500 g) neonates died after the use of intravenous vitamin E preparation. The cause of death was associated with polysorbate 80 used as a solubilising agent in the preparation.^{10,11}

The main groups of harmful excipients (HEs) are:

- ▶ antimicrobial preservatives (benzalkonium chloride, benzoic acid, benzyl alcohol, sodium benzoate and parabens);
- ▶ solubilising agents (polysorbate 80);
- ▶ solvents (ethanol and propylene glycol);
- ▶ sweetening agents (saccharin sodium and sorbitol).

Excipients, analysed in our study, were chosen according to the Nellis *et al* study.¹² The HE effects have been reported in previous publications (Rowe 2009,⁸ EMA 2003,⁹ Nellis *et al* 2015,¹² Lass *et al* 2012,¹³ etc). For instance, polysorbate 80 may cause E-ferol syndrome. Benzalkonium chloride might be ototoxic when applied to an ear.^{8,12,13} Benzoic acid may increase the risk of jaundice in newborn babies, hypersensitivity and kernicterus.^{9,12} Medicines with benzyl alcohol may result in headache, vomiting, diarrhoea,^{8,13} metabolic acidosis, seizures, gasping,^{12,13} hypersensitivity,¹³ kernicterus

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and intraventricular haemorrhage.¹² Premature infants may have fatal toxic syndrome.^{12–13} Parabens may cause hyperbilirubinaemia,^{12–13} hypersensitivity reactions,^{8–9–12–13} oestrogenic effects (propylparaben)¹² and delayed-contact dermatitis.⁸ Neonates who use medicines with sodium benzoate may have hypersensitivity, kernicterus¹² and contact urticaria.^{8–9–13} Propylene glycol may cause skin irritation,^{8–9–12–13} central nervous system depression, cardiovascular adverse events,^{8–12–13} hepatic adverse events, respiratory adverse events,^{12–13} hyperosmolality,^{8–12} lactic acidosis,^{8–12} alcohol-like symptoms (oral, parenteral),⁹ ototoxicity, seizures and contact dermatitis.⁸ Medicines with ethanol may result in lactic acidosis, hypoglycaemia¹² and CNS effects.^{12–13} Sorbitol can cause diarrhoea^{9–12} and nutrient malabsorption,¹² and saccharin sodium – urticaria and photosensitivity.^{12–13}

No official guidelines are available advising which excipients should not be used in neonatal medications. There are some general guidelines—for example, ‘Excipients in the label and package leaflet of medicinal products for human use’⁹ or ‘Guideline on the investigation of medicinal products in the term and preterm neonate’,⁷ and pharmaceutical excipients handbooks describing general safety data.⁸ Probably, the European Study of Neonatal Exposure to Excipients (ESNEE) project¹⁴ and the database of ‘Safety and Toxicity of Excipients for Paediatrics’¹⁵ will improve this situation. The ESNEE project was created in order to provide information about the safety of excipients in neonatal medicines. The members of the project group have published some valuable articles—for example, a systematic review of excipients safety.¹⁶ There are also articles focused on risk assessment with regard to neonatal excipient exposure¹⁷ or excipients’ safety.¹⁸ Some authors have analysed pharmacokinetic of specific excipients—for example, propylene glycol^{19–21} and benzyl alcohol.²² Despite some recent pan-European^{12–23} and local (country)^{13–24–27} studies on excipients used in neonates, there is still a lack of studies in this field. Our main aim was to analyse the frequency of using HEs in hospitalised neonates in the Department of Neonatology; and then, to identify possibility of substituting for medicines containing HEs.

METHODS

This retrospective observational cohort study was performed at the University Children’s Hospital in Riga, Latvia. This is a multi-specialty university paediatric hospital with approximately 500 beds. The Department of Neonatology has an intensive care unit (NICU) and a neonatal ward. Hospitalised neonates who received a prescription for medicines containing an HE were included in the study. Most of these patients (all preterm babies) were admitted to the NICU. The study lasted from 1 September 2015 to 29 February 2016. The following information was collected from the patients’ medical records by a clinical pharmacist: demographic data (date of birth, gender, gestational age, birth weight), admission and discharge dates, prescribed medicines, dosages and the route of administration. Neonates were divided into four groups according to the gestational age (<28 weeks, called extremely preterm; 28 to <32 weeks, very preterm; 32 to <37 weeks, late preterm and ≥37 weeks, term neonates)^{12–28} as the severity and type of complications of preterm infants may be directly proportional to neonatal immaturity and their physiological status.²⁹ All medicines and food supplements prescribed to hospitalised neonates were analysed, except for blood products, glucose and electrolyte solutions, vaccines, parenteral nutrition products and contrast agents. Each medicine was classified according to the international non-proprietary name, trade name, pharmaceutical dosage form, strength and route of administration.

Identification of excipients

In this study 12 excipients that have been associated with toxicity in neonates¹² were chosen to see if they were included in any of the medicines prescribed. We chose to analyse the same excipients that were investigated in the recent pan-European point prevalence study.¹² These excipients were benzalkonium chloride, benzyl alcohol, benzoic acid, ethanol, ethyl-, methyl- and propylparahydroxybenzoate, polysorbate 80, propylene glycol, saccharin sodium, sodium benzoate and sorbitol. Excipients and the amount of each HE (if available) were identified from their Summaries of Product Characteristics (SPC) and/or the home pages of manufacturers.

Products’ substitution analysis

Substitution was determined according to criteria described in the Nellis *et al* analysis: ‘stage 1 – medicines could be substituted with a product with the same active pharmaceutical ingredient and route of administration; stage 2 – stage 1 plus requirement of identical dosage form; stage 3 – stages 1 and 2 plus requirement of identical strength of the active pharmaceutical ingredient.’²³ Only those products not containing any harmful excipient were considered for valid substitution in the analysis.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 20.0 statistical software package (SPSS Inc, USA) and Microsoft Excel programs. Patients’ data were analysed using descriptive statistical methods (percentage proportion, mean and SD). Nominal data were described as the quantity (n) and percentage with 95% CI. Categorical data were analysed with χ^2 test (2×2 tables). Data with p value <0.05 were regarded as statistically significant. Categorical data were also described as the quantity and percentage proportion.

The study used anonymised data and did not require individual consent from parents. The local ethics committee approved the study’s protocol.

RESULTS

During the period of study 327 neonates were hospitalised. Thirty-one (9.5%) patients (5 late preterm neonates and 26 term neonates) did not receive medicines containing the HE excipients that were being examined and were excluded from the study. The 296 neonates (102 (34.5%) preterm) included in the study received 1472 prescriptions for 106 medicines (table 1) and six food supplements.

The smallest percentage of patients receiving HEs was in the term neonates’ subgroup (118/194, 60.8%). In late preterm neonates’ subgroup 72.1% of neonates received medications with HEs. The highest percentage of patients was in the extremely preterm and very preterm neonates’ subgroups: 100% and 96.2% of patients, respectively. There was a difference between genders in the subgroups of patients who received or had not received HEs. Nevertheless, this difference was not statistically significant (χ^2 test; table 1).

There were 144 prescriptions for food supplements. Food supplements did not contain HEs and were excluded from further study. The most often used formulations were intravenous (48/106; 45.3%), oral solid formulations, such as crushed tablets or opened capsules (20; 18.9%), and topical formulations, such as creams, ointments and topical solutions (16; 15.1%). Oral liquids (9; 8.5%), ophthalmic formulations (6; 5.7%), inhalation medicines (3; 2.8%), nasal formulations (2;

Table 1 Demographic characteristics of neonates admitted to the Department of Neonatology

Characteristics	Extremely preterm	Very preterm	Late preterm	Term
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Neonates	8 (2.7) (0.9 to 4.6)	26 (8.8) (5.6 to 12.0)	68 (23.0) (18.2 to 27.8)	194 (65.5) (60.1 to 70.9)
Gestational age, weeks (mean $\pm$ SD)	25 $\pm$ 1.2 (23 to 27)	30 $\pm$ 1.2 (28 to 31)	34 $\pm$ 1.5 (32 to 36)	40 $\pm$ 1.5 (37 to 50)
Birth weight (g)	937 (620 to 1284)	1474 (880 to 2290)	2258 (930 to 3900)	3524 (1760 to 5038)
Gender				
Female	4 (50.0)	11 (42.3)	30 (44.1)	83 (42.8)
Female receiving HEs	4 (100)	11 (100)	23 (76.7)	49 (59.0)
Male	4 (50.0)	15 (57.7)	38 (55.9)	111 (57.2)
Male receiving HEs	4 (100)	14 (93.3)	26 (68.4)	69 (62.2)

Abbreviation: HEs, harmful excipients.

1.9%), rectal formulations (1; 0.9%) and subcutaneous formulations (1; 0.9%) were rarely used (table 2).

Information on excipients was available for all 106 medicines. The total number of different excipients was 169. In total, 29/106 (27.4%) medicines contained at least one HE (figure 1). None of these preparations contained benzoic acid and ethylparabens. Parenteral formulations were the most often used. In total, there were 558 (42.0%) parenteral prescriptions, but only seven (17.1%) medicines contained HE (figure 1). These excipients were benzyl alcohol (3; 42.9% formulations), ethanol (2; 28.6%), methylparahydroxybenzoate (3; 42.9%), propylparahydroxybenzoate (2; 28.6%), propylene glycol (3; 42.9%) and sorbitol (1; 14.3%).

The amount of the HEs was not available in the SPC for 13/29 (44.8%) products. The exact amount of benzalkonium chloride was available in 2 out of 7 medicines in the SPC, benzyl alcohol – 1 of 4, ethanol – 1 of 3, methylparahydroxybenzoate – 1 of 8, sodium benzoate – 1 of 3, propylene glycol – 2 of 4, propylparahydroxybenzoate – 1 of 7, saccharin sodium – 1 of 4 and sorbitol – 2 of 5 medicines. No information was available about the exact amount of polysorbate 80 in all four medicines used during the period of study. Four HEs were found in two products, three HEs in two products, two

HEs in eight products, and one HE in 16 products. In total, 82/102 (80.4%) preterm and 118/194 (60.8%) term neonates received medications with at least one HE. Only 5 (17.2%) medicines were licensed for use in neonates (table 3).

According to Nellis *et al*²³ first-stage criteria substitution was possible for 9/29 (31.0%) HE-containing medicines. By adding the second and third stages, the possibility of medicines' substitution was reduced to 7/29 (24.1%) and 4/29 (13.8%), respectively (table 3). For instance, it is possible to substitute ibuprofen oral suspension (contains methyl- and propylparahydroxybenzoate) with ibuprofen tablets that do not contain HEs (first-stage criteria substitution). Also, it is possible to substitute dexpanthenol cream (contains propylene glycol) with dexpanthenol ointment that does not contain HEs (second-stage criteria substitution), and pyridoxine injection 50 mg/mL (contains methylparahydroxybenzoate) with pyridoxine injection 50 mg/mL without HEs (third-stage criteria substitution).

DISCUSSION

Our study shows that hospitalised neonates in Latvia receive medicines containing HEs, but medicines' substitution was possible in only a small number of cases. Thus, the main focus should be

Table 2 Number of prescriptions and HEs prescribed by route of administration according to gestational age category

Characteristics	Extremely preterm	Very preterm	Late preterm	Term
	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
Prescriptions (total n)	105	206	315	846
Prescriptions without food supplements (total n=1328)	99 (94.3) (89.9 to 98.7)	184 (89.3) (85.1 to 93.5)	271 (86.0) (82.2 to 89.8)	774 (91.5) (89.6 to 93.4)
Prescriptions with HEs and without food supplements (total n)	31 (31.3) (22.2 to 40.4)	65 (35.3) (28.4 to 42.2)	88 (32.5) (26.9 to 38.1)	188 (24.3) (21.3 to 27.3)
Intravenous	37 (37.4)	64 (34.8)	112 (41.3)	345 (44.6)
Intravenous (with HEs)	4 (10.8)	13 (20.3)	28 (25.0)	50 (14.5)
Inhalation	13 (13.1)	14 (7.6)	8 (3.0)	67 (8.7)
Inhalation (with HEs)	11 (84.6)	12 (85.7)	8 (100)	43 (64.2)
Oral	44 (44.5)	87 (47.3)	114 (42.1)	211 (27.3)
Oral (with HEs)	12 (27.3)	31 (35.6)	29 (25.4)	33 (15.6)
Topical	1 (1.0)	12 (6.5)	17 (6.2)	72 (9.3)
Topical (with HEs)	1 (100)	3 (25.0)	4 (23.5)	15 (20.8)
Other	3 (3.0)	7 (3.8)	20 (7.4)	83 (10.7)
Other (with HEs)	3 (100)	6 (85.7)	19 (95.0)	47 (56.6)

HEs, harmful excipients.

Figure 1 Number of medicines with and without HE excipients Figure 1 87x50mm (600 x 600 DPI).

on providing information and education for hospital specialists about HEs and their possible adverse reactions. The proportion of medicines containing HEs in our study (27.4%) was almost the same as that reported by Nellis *et al.*¹² (31.0%), but lower than in the study published by Lass *et al.*¹³ (68.0%). The difference from the latter study might be explained by differences in methodology (eg, we did not include analysis of medicines potentially containing HEs in our study). The number of neonates receiving at least one HE was also similar to that reported by Nellis *et al.*¹² Our study shows that the medicines' substitution was possible in only a small number of cases as compared with the study of Nellis *et al.*²³ This might be because the Latvian market is small. In accordance with local legislation (Regulations of Minister Cabinet from 31 October 2006 No. 899 'Procedures for the Reimbursement of Expenditures for the Acquisition of Medicinal Products and Medicinal Devices Intended for Out-patient Medical Treatment'), the cheapest product must be purchased. Another problem is that these 12 HEs are not mentioned in any European regulation or directive and there are only a few recommendations by specialists as to how to avoid using these excipients in neonates. The results from existing studies may not be sufficiently strong to allow purchase of another HE-free product which has a higher price than the product containing HEs.

Collaboration between stakeholders at the local and European level is required to solve the various problems associated with substitution, such as availability of quantitative data of HEs, toxicological assessment of excipients and substitution costs. Unavailability of suitable formulations for paediatric use may lead pharmacists to prepare extemporaneous liquid preparations. Stability data and the safety of excipients are some of the problems that pharmacists must solve before such preparation.³⁰ Our hospital pharmacists do prepare some oral solutions—for example, phenobarbital solution with SyrSpend SF PH4 (liquid) or caffeine water solution. Phenobarbital solution should not be used in neonates because the syrup contains sodium benzoate. Caffeine solution does not contain preservatives, and therefore has a very short shelf-life. Some excipients may not be required for some formulations—for example,

antimicrobials for parenteral formulations.¹² In our study 46/53 (86.8%) parenteral formulations and 463 parenteral prescriptions (83.0%) had no HEs. These results are similar to the results of Nellis *et al.* In their study 85% of parenteral prescriptions did not have parabens and benzoates, which means that these preservatives could be avoided.¹²

Substitution was not possible for two medicines (gentamicin and phenobarbital), which are widely used in neonates. According to European Medicines Agency (EMA) guidelines 'inclusion of antimicrobial preservatives in a medicinal product needs special justification. Wherever possible the use of these substances should be avoided, particularly in paediatric formulations'.³¹ In our study parenteral medicines contained benzyl alcohol, ethanol, methyl- and propylparahydroxybenzoate, propylene glycol and sorbitol (table 3). In total, 19 (65.5%) medicines contained antimicrobial preservatives. Sweeteners should be used with caution as they may cause diarrhoea,^{9 12} nutrient malabsorption (sorbitol),¹² urticaria and photosensitivity (saccharin sodium).^{12 13} Sorbitol may have laxative effect that should be considered along with its osmotic properties and potential effects on bioavailability.⁶ In our study 10 patients received sorbitol (whereas in the Nellis *et al* study, no patients received a sorbitol-containing formulation) and two patients received medications with saccharin sodium. We found no substitution possibilities for the oral medicines that were used in our study which did not contain sweeteners. For one parenteral formulation (clemastine) it was possible to substitute a therapeutic alternative (chloropyramine) that did not contain HEs. Nevertheless, we would need more information about why clemastine was being used before making the substitution. Most of the medicines containing HEs were not licensed for use in neonates (table 3). Most of them are off-patent drugs and there is probably limited interest by industry in developing 'paediatric friendly' formulations for these active substances, as such research might be expensive and profit small. Also, parents may not agree to their children participating in clinical studies and there might be too few patients to allow comprehensive conclusions to be reached.

Table 3 Medications containing harmful excipients(HE), availability of HEs-free products in Latvia and prescriptions to neonates

Medications containing HEs	Excipient	Product substitution	Licensed for use in neonates	Extremely preterm n=31 (%)	Very preterm n=65 (%)	Late preterm n=88 (%)	Term n=188 (%)
Gentamicin injection	Methyl- and propylparahydroxybenzoate	Not available	Yes [†]	3 (9.7)	13 (20.0)	29 (33.0)	41 (21.8)
Simethicone oral suspension [†]	Sorbitol	Not available	No	2 (6.5)	7 (10.8)	15 (17.0)	17 (9.0)
Salbutamol nebulisation solution	Benzalkonium chloride [‡]	No substitution available for the 5 mg/mL solution	?	6 (19.4)	6 (9.2)	3 (3.4)	23 (12.2)
Iron oral solution	Ethanol [‡] , methyl- and propylparahydroxybenzoate [‡] , sorbitol [‡]	A few products without HEs are available, but they are subject to additional monitoring or do not have appropriate strength or formulation	Yes	8 (25.8)	20 (30.8)	7 (8.0)	2 (1.1)
Budesonide nebulisation suspension	Polysorbate 80 [‡]	Not available	No	5 (16.1)	6 (9.2)	5 (5.7)	20 (10.6)
Chloramphenicol ophthalmic solution	Benzalkonium chloride, polysorbate 80 [‡]	Not available	No	1 (3.2)	2 (3.1)	4 (4.5)	21 (11.2)
Tobramycin, dexamethasone ophthalmic solution	Benzalkonium chloride	Another formulation (ointment) is available	No	1 (3.2)	2 (3.1)	6 (6.8)	9 (4.8)
Phenylephrine, dimethindene maleate nasal spray	Benzalkonium chloride [‡] , sorbitol [‡]	Not available	No	0	2 (3.1)	5 (5.7)	5 (2.7)
Simethicone oral suspension [†]	Saccharin sodium	Not available	No	0	2 (3.1)	2 (2.3)	6 (3.2)
Miconazole oral gel [¶]	Ethanol	Not available	No	0	1 (1.5)	2 (2.3)	7 (3.7)
Tobramycin ophthalmic solution	Benzalkonium chloride	Another formulation (ointment) is available	No	1 (3.2)	0	3 (3.4)	6 (3.2)
Phenobarbital injection ^{¶¶}	Ethanol, propylene glycol	Not available	No	1 (3.2)	0	0	6 (3.2)
Dexpanthenol cream	Propylene glycol [‡]	Another formulation (ointment) is available	No	0	0	0	5 (2.7)
Phosphate tablets [¶]	Saccharin sodium [‡]	Not available	?	2 (6.5)	1 (1.5)	2 (2.3)	0
Troxerutin gel	Benzalkonium chloride [‡]	Not available	No	0	0	1 (1.1)	3 (1.6)
Diosmectide powder for oral suspension	Saccharin sodium [‡] , ethanol [‡]	Not available	No	0	0	0	4 (2.2)
Clotrimazole ointment	Benzyl alcohol [‡]	Not available	No	0	2 (3.1)	1 (1.1)	0
Zidovudine oral solution	Sodium benzoate	Not available	No	0	0	2 (2.3)	1 (0.5)
Amphotericin B oral suspension [¶]	Methyl- and propylparahydroxybenzoate [‡] , saccharin sodium [‡]	Not available	Yes	0	0	1 (1.1)	1 (0.5)
Diclofenac injection	Benzyl alcohol, propylene glycol	Available	No	0	0	0	2 (1.1)
Pyridoxine injection	Methylparahydroxybenzoate	Available	Yes	0	0	0	2 (1.1)
Heparin injection	Benzyl alcohol	Available	No	0	0	0	2 (1.1)
Sulfamethoxazole, Trimethoprim oral syrup	Methyl- and propylparahydroxybenzoate [‡] , polysorbate 80 [‡] , sorbitol [‡]	Oral suspension is not available Tablets (different strength) with fewer HEs available	No	0	0	0	1 (0.5)
Clemastine injection	Ethanol, propylene glycol, sorbitol	Parenteral formulation is not available HE-free tablets available	No	0	0	0	1 (0.5)
Dialysatum deproteinatum sanguinis vituli ointment	Methyl- and propylparahydroxybenzoate	Not available	No	1 (3.2)	0	0	0
Azithromycin tablets	Polysorbate 80 [‡]	Available HE-free powder for oral suspension and tablets are available	No	0	1 (1.5)	0	0
Ciprofloxacin ophthalmic solution	Benzalkonium chloride	Not available	Yes	0	0	0	1 (0.5)

Continued

Table 3 Continued

Medications containing HEs	Excipient	Product substitution	Licensed for use in neonates	Extremely preterm n=31 (%)	Very preterm n=65 (%)	Late preterm n=88 (%)	Term n=188 (%)
Methylprednisolone injection	Benzyl alcohol	Tablets do not contain HEs HE-free parenteral formulation (different strength) is available	No	0	0	0	1 (0.5)
Ibuprofen oral suspension	Methyl- and propylparahydroxybenzoate	HE-free tablets and a parenteral formulation available	No	0	0	0	1 (0.5)

*Both formulations are licensed for use in neonates.

†Two different simethicone oral solution products were used.

‡There was no amount of the excipient available in the SPC

§Nothing is written about neonates – the text is ‘children under 12 years’.

¶Not registered in the Latvian market.

**None of the formulations (eg, parenteral, oral) is registered in the Latvian market.

††Nothing is written about neonates – the text is ‘children under 5 years’.

No information on adverse reactions due to HEs was found in patients' records; possibly, because physicians had not been warned before the study about such a possibility. Additionally, during the study no adverse reactions were identified. Possibly, the usage of HEs did not reach the toxic level. Calculations of HE intakes might be the next step of this research, although this would not be possible in all cases because the exact amounts of HEs used in specific formulations was not contained in all SPC leaflets. Probably not all pharmaceutical companies are interested in sharing the data. Accepted daily intakes have been reported for some excipients—for example, sodium benzoate daily intake should not exceed 10 mg/kg owing to immature metabolic capability. However, information about a safe dose of a specific excipient is not always available—for example, the EMA has no recommendations on a safe dose for propylene glycol.³² Different doses are mentioned in the EMA's overview of 22 publications.

We have initiated discussions with the hospital Drug and Therapeutic Committee about the possibility of purchasing HE-free medicines for neonates if such products are available. As a result, local medication registration prices could be reduced for some specific medications for specific patient groups—for example, HE-free formulations for neonates. Perhaps it would be more attractive for pharmaceutical companies to register such medications in countries with small markets. However, collaboration between stakeholders is required to solve the different problems concerning registration of medicines. Meanwhile, the clinical pharmacist has prepared leaflets and local recommendations on the hospital intranet for doctors containing warnings about currently used medicines with HEs. There is also information about the HEs that these products contain and possible adverse reactions. Discussion is continuing with the hospital pharmacy about the possibility of preparing oral solutions without HEs for neonates. The EMA recommends the avoidance of preservatives, antioxidants, etc, and the use of sterile products to eliminate microbial contamination.⁷

LIMITATIONS

First, the study period was 6 months and it is possible that not all products containing HEs were identified. Therefore, the clinical pharmacist is reviewing the hospital drug formulary in order to identify other medicines with HEs that might be used in neonates. Second, the study analysed only HEs, and not other excipients known as ‘potentially HE’ (eg, sodium metabisulfite, disodium edetate). Third, not all SPCs had quantitative information on excipients. Therefore, it was not possible to analyse the amount of excipients that neonates received. We agree with

Nellis *et al*^{12 15 23} that quantitative information on excipients is needed before considering a switch from one product to another.

CONCLUSIONS

Neonates in Latvia receive a number of HEs. The use of these excipients can be reduced by using HE-free products available on the European market. However, the possibility of reducing use of these excipients in the hospital is limited owing to the lack HE-free formulations available on the local market, as well as local legislation.

Contributors Both authors have contributed significantly to the publication.

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REFERENCES

- Marek E, Kraft WK. Ethanol pharmacokinetics in neonates and infants. *Curr Ther Res Clin Exp* 2014;76:90–7.
- Whittaker A, Currie AE, Turner MA, *et al*. Toxic additives in medication for preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F236–40.
- Alade SL, Brown RE, Paquet A Jr. Polysorbate 80 and E-Ferol toxicity. *Pediatrics* 1986;77:593–7.
- Masi S, de Cléty SC, Anslot C, *et al*. Acute amiodarone toxicity due to an administration error: could excipient be responsible? *Br J Clin Pharmacol* 2009;67:691–3.
- Fabiano V, Mameli C, Zuccotti GV. Paediatric pharmacology: Remember the excipients. *Pharmacol Res* 2011;63:362–5.
- European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev 2. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf (accessed 5 May 2016).
- European Medicines Agency. Guideline on the investigation of medicinal products in the term and preterm neonate. 2009. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003754.pdf (accessed 5 May 2016).
- Rowe RC. *Handbook of pharmaceutical excipients*. 6th Edition: Pharmaceutical Press, 2009:888.
- European Commission. Excipients in the label and package leaflet of medicinal products for human use. 2003. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf (accessed 28 Feb 2016).
- Phelps DL. E-ferol: what happened and what now? *Pediatrics* 1984;74:1114–6.
- Lucy JF. Do you remember E-Ferol? the penalty for selling untested drugs in neonatology: fines and a jail sentence. *Pediatrics* 1992;89:159.
- Nellis G, Metsvaht T, Varendi H, *et al*. Potentially harmful excipients in neonatal medicines: a pan-European observational study. *Arch Dis Child* 2015;100:694–9.
- Lass J, Naelapää K, Shah U, *et al*. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. *BMC Pediatr* 2012;12:136.
- Turner MA, Duncan J, Shah U, *et al*. European Study of neonatal Exposure to Excipients: an update. *Int J Pharm* 2013;457:357–8.

- 15 Salunke S, Tuleu C; European Paediatric Formulation Initiative (EuPFI). The STEP database through the end-users eyes--USABILITY STUDY. *Int J Pharm* 2015;492:316–31.
- 16 Vaconsin P, Storme T, Salunke S, *et al.* Esnee project: strategy for the extensive review of the literature on excipient toxicities. *Eur J Hosp Pharm* 2012;19:1–183.
- 17 Turner MA, Duncan JC, Shah U, *et al.* Risk assessment of neonatal excipient exposure: lessons from food safety and other areas. *Adv Drug Deliv Rev* 2014;73:89–101.
- 18 Nahata MC. Safety of "inert" additives or excipients in paediatric medicines. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F392–3.
- 19 Kulo A, de Hoon JN, Allegaert K. The propylene glycol research project to illustrate the feasibility and difficulties to study toxicokinetics in neonates. *Int J Pharm* 2012;435:112–4.
- 20 Allegaert K, Vanhaesebrouck S, Kulo A, *et al.* Prospective assessment of short-term propylene glycol tolerance in neonates. *Arch Dis Child* 2010;95:1054–8.
- 21 De Cock RF, Knibbe CA, Kulo A, *et al.* Developmental pharmacokinetics of propylene glycol in preterm and term neonates. *Br J Clin Pharmacol* 2013;75:162–71.
- 22 Shehab N, Lewis CL, Streetman DD, *et al.* Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. *Pediatr Crit Care Med* 2009;10:256–9.
- 23 Nellis G, Metsvaht T, Varendi H, *et al.* Product substitution as a way forward in avoiding potentially harmful excipients in neonates. *Pediatric Drugs* 2016;18:221–30.
- 24 García-Palop B, Movilla Polanco E, Cañete Ramirez C, *et al.* Harmful excipients in medicines for neonates in Spain. *Int J Clin Pharm* 2016;38:238–42.
- 25 de Souza AS, Dos Santos DB, Rey LC, *et al.* Off-label use and harmful potential of drugs in a NICU in Brazil: A descriptive study. *BMC Pediatr* 2016;16:13.
- 26 Fister P, Urh S, Karner A, *et al.* The prevalence and pattern of pharmaceutical and excipient exposure in a neonatal unit in Slovenia. *The Journal of Maternal-Fetal & Neonatal Medicine* 2015;28:2053–61.
- 27 van Riet-Nales DA, de Jager KE, Schobben AF, *et al.* The availability and age-appropriateness of medicines authorized for children in the Netherlands. *Br J Clin Pharmacol* 2011;72:465–73.
- 28 World Health Organization. Preterm birth. Fact sheet N°363. <http://www.who.int/mediacentre/factsheets/fs363/en/> (accessed 12 Dec 2015).
- 29 Behrman RE, Butler AS, eds. *Preterm birth: causes, consequences, and prevention*. Washington DC: National Academies Press, 2007. <http://www.ncbi.nlm.nih.gov/books/NBK11382/> (accessed 16 Jun 2016).
- 30 Balan S, Hassali MA, Mak VS. Challenges in pediatric drug use: A pharmacist point of view. *Res Social Adm Pharm* 2016. pii: S1551-7411(6)30201-7.
- 31 EMA. Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. 2007 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003382.pdf (accessed 2 Dec 2016).
- 32 Propylene glycol in medicinal products for children. Assessment report. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/03/WC500163989.pdf (accessed 2 Dec 2016).