www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2018;7(1):e070112
doi: 10.7363/070112
Received: 2017 May 10; accepted: 2017 Jul 28; published online: 2017 Dec 24

Review

Neonates exposed to excipients: concern about safety

Laura Cuzzolin

Department of Diagnostics & Public Health – Section of Pharmacology, University of Verona, Verona, Italy

Abstract

Excipients are generally perceived as inert and pharmacologically inactive. Instead, serious adverse reactions have been reported in vulnerable patient populations and little is known about exposure of newborns to excipients. The aim of this review is to deepen the presence of potentially harmful excipients in drugs commonly used in neonates. From an analysis of articles and case reports present in the international literature emerges that several medicines administered to newborns contain potentially harmful excipients such as ethanol, propylene glycol and benzyl alcohol. Neonatologists should be aware of this problem and possibly prescribe substitutive treatments.

Keywords

Excipients, newborns, safety.

Corresponding author

Laura Cuzzolin, Department of Diagnostics & Public Health – Section of Pharmacology, University of Verona, Verona, Italy; tel.: +39 045 8027609; fax: +39 045 8124876; e-mail: laura.cuzzolin@univr.it.

How to cite

Cuzzolin L. Neonates exposed to excipients: concern about safety. J Pediatr Neonat Individual Med. 2018;7(1):e070112. doi: 10.7363/070112.

Introduction

Due to their unique physiology, neonates are particularly vulnerable to drug treatments and the effects of active compounds and excipients present in pharmaceutical preparations can be different compared to children and adults [1].

Usually, the interest about safety is focused on active compounds and excipients are supposed to be pharmacologically inactive [2]. Instead, certain

excipients present in medicines commonly used in the neonatal population are currently recognised as toxic to newborns if they are given at high doses [3-6] and occasional reports referred serious adverse events in neonates [7-10]. Taking into account that critically ill newborns admitted to NICUs receive many medicines and then may be exposed to different excipients per day, this merits great concern suggesting that also excipients should be labelled with sufficient composition information and excipient-free formulations should be considered whenever possible [3, 4].

In this article we will give an updated overview of the worldwide situation in the neonatal population as regards the exposure to excipients potentially harmful. For this reason, some considerations about availability of formulations for neonates will be discussed and an analysis of the literature will be made.

Excipients and age-appriopriateness of formulations for neonates

With the term excipient we refer to every inert agent present in a formulation (solvents, diluents, emulsifiers, preservatives, sweeteners...) added with the scope to confer shape, volume and consistency to the pharmaceutical preparation, to stabilize the active drug, to enable its bioavailability and deliver the active principle to its site of action, to ensure an easy administration and favouring the compliance [2].

Usually, safety data available for excipients derive from adults, while information in neonates and children is often missing [11]. Excipients that have not caused problems in adults are assumed to be safe in neonates, despite significant differences in pharmacokinetics and pharmacodynamics [6].

The Committee for Medicinal Products for Human Use guideline about excipients states that "*excipients to be used in formulations for the paediatric population should be selected with special care and possible sensitivities of the different age groups should be taken into consideration*" [12]. Despite this, while since 2010 new medications authorized in Europe have to specify quantitative details of excipients in the Summary of Product Characteristics (SPCs) [13], many paediatric formulations licensed before the European Pediatric Regulation contain excipients not recommended for use in neonates [14]. In addition, many drugs administered to neonates are still not licensed for this paediatric subpopulation leading to a common use of extemporaneous or magistral preparations and off-label medications in absence of suitable commercial formulations [15].

The development of feasible formulations represents a challenge for the neonatal population, characterized by unique needs. Many drugs used in newborns do not exist in a suitable dosage form to allow administration to a neonate. Therefore, adult formulations need to be manipulated to obtain an age-appropriate product. This implies that some excipients should be added to the original product for many reasons, for example to stabilise the new formulation or to make it palatable [6]. A drug should have a good taste to ameliorate palatability of oral liquid formulations and parenteral preparations should contain small dose volumes and should be administered using small needles [2]. To achieve this, a lot of excipients are commonly used in paediatric formulations, exposing particularly neonates and infants, characterized by a different pharmacokinetic behaviour, to potentially serious adverse events. The European Medicines Agency (EMA) reflection paper states that "manipulation of adult medicinal products for paediatric use should be the last resort", but at the same time underlines that "this is recognized as an unavoidable and necessary operation in many cases" [16].

In the Netherlands, about half of the oral liquid preparations and 7% of the parenteral formulations contain potentially harmful excipients [17], favouring the use of unlicensed preparations. Therefore, the choice of excipients and of their dosage is a major challenge that should be justified through a risk-based assessment, taking into account different factors including the convenience of administration and the flexibility of the dosage form: in a paediatric formulation, the number of excipients and their level should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, dose uniformity [18]. The European Study of Neonatal Exposure to Excipients (ENSEE) aims to provide an evidence base for discussion about the safety of medicines given to newborns by determining the exposure of neonates to excipients, comparing variations within and between regions, and measuring concentrations of excipients in the blood of babies routinely treated [19].

Surely, medicines containing excipients have benefits and these benefits in many cases will not be possible in absence of excipients. However, any excipient present in a formulation should not pose unacceptable risks for the neonate [4]. For

identification of excipients in each medication, the SPCs is the best available source.

Excipients potentially harmful for neonates

A wide range of excipients has been related to potential harm in neonates, even if a limited number of these harms resulted fatal or disabling.

Solvents such as ethanol and propylene glycol are often present in formulations for newborns and infants to improve drug solubility.

Ethanol is found in many oral liquid preparations (for example furosemide and ranitidine preparations, iron supplementations) and together with its metabolite acetaldehyde could have synergic negative effects on central nervous system, as observed when in association with dextromethorfan, present in an over-the-counter (OTC) cough syrup [20]. In Italy [21] and in the UK [14, 22], many commercially available preparations for neonates have the potential to deliver significant amounts of ethanol and other authors found that 14 formulations routinely used in NICUs contain ethanol [23]. The U.S. Food and Drug Administration (FDA) issued a guidance on the ethanol content of OTC medications indicating in 0.5% the maximum concentration for subjects under 6 years [24], while the EMA published a draft for the guideline on "*Excipients in the label and package leaflet of medicinal products for human use*" containing detailed information on ethanol content, comprised thresholds for different age groups [25].

Propylene glycol, a solvent with antimicrobial properties, is one of predominant excipients present in medications routinely administered to critically ill neonates. High doses of propylene glycol have been associated with respiratory, cardiovascular, central and hepatic adverse effects in newborns [26, 27] probably due to accumulation of propylene glycol and its metabolites in presence of limited hepatic and renal elimination capacity [28]. A FDA drug safety communication underlined serious health problems in preterm neonates exposed to an oral solution of lopinavir/ritonavir containing propylene glycol [29]. This solvent is present in dexamethasone preparations, commonly used in NICUs to treat chronic pulmonary disease, in concentrations that largely exceed the acceptable intake limit for adults [14, 30]. Sources of intravenous propylene glycol exposure in neonates regard also other drugs such as diazepam, digoxin, lorazepam, nitroglycerin and phenobarbital [31].

Exposure to peanut oil, present as solvent in intramuscular injections and in topical formulations for the prevention and treatment of the genital dermatitis, could lead to episodes of hypersensitivity [2].

The use of preservatives in medicines intended for newborns requires special consideration and preservative-free formulations should be considered whenever possible.

Among preservatives, benzalkonium chloride, frequently present in beclometasone and ipratropium bromide nebulizer solutions and in topical medications such as nasal saline and decongestants, has been associated with bronchospasm in paediatric patients [32].

Another commonly used preservative is benzyl alcohol, known to determine metabolic acidosis, seizures and gasping. Benzyl alcohol partially undergoes hepatic oxidative metabolism to benzoic acid: a reduced metabolic capacity to inactivate benzoic acid to hippuric acid has been suggested as the underlying mechanism of benzyl alcohol toxicity in newborns [33]. Intravenous formulations of some corticosteroids (betamethasone and triamcinolone) contain benzyl alcohol, contraindicated in newborns as it can induce anaphylactic reactions under 3 years of life [34] and the routine use of continuous infusions of benzodiazepines, including midazolam, in this patient population is currently not recommended [35]. In the early 1980s, benzyl alcohol has been also associated to a neonatal toxic syndrome attributed to the practice of flushing out umbilical catheters with solutions containing this substance and characterized by CNS depression, respiratory distress and severe metabolic acidosis [36]: as a consequence, the FDA recommended that fluids containing benzyl alcohol had not to be used in preterm newborns.

The safety assessment of parabens present in pediatric oral formulations needs to take into account their beneficial antimicrobial effects, so their withdrawal may increase the risk of infection in neonates. However, while acceptable daily intake has been established for adults [37], this has not been assigned to neonates. Recently, the presence of parabens in blood circulation of 196 neonates from the UK and Estonia confirm a systemic exposure to these compounds following administration of routine medicines [38]: this is of concern, being the exposure at high doses associated to hyperbilirubinemia and oestrogenic effects [6].

Antioxidants such as sulfites should be responsible for the development of symptoms such as wheezing or dyspnoea and non-immunologic anaphylactoid reactions have also been reported [39]: for these reasons, inhaled formulations for asthmatic subjects have been revised by eliminating the presence of sulfites. Sodium metabisulphite (present in oral, parenteral and topical formulations) is found in inotropes such as dopamine and dobutamine, commonly used to treat haemodynamic insufficiency in the first days of life, to maintain the stability of these molecules [40].

Another important aspect regards the use of natural or artificial sweeteners to modify the organoleptic properties of paediatric formulations, with the aim to improve palatability and compliance (for example multivitamins and domperidone oral solutions). Among the natural sweeteners, lactose and sorbitol may cause gastrointestinal symptoms in intolerant subjects [41], while sucrose is potentially cariogenic [42]. As regards artificial sweeteners, aspartame as a source of phenylalanine may be harmful in subjects affected by phenylchetonuria [43] and has been associated with headache and seizures [44], while saccharin could increase the risk of developing cancer or dermatological reactions [45]. The use of sweetening agents in formulations for neonates is not recommended due to a lack of established safety data [2].

Finally, pharmaceutical products contain different "E number" additives, including artificial colourants, that could have a negative impact on children behaviour or could lead to anaphylactoid reactions [2].

Literature data

From the analysis of the literature, limited to a relatively few number of articles (**Tab. 1**), emerges that almost all drugs used in neonates (including those licensed) contain at least one potentially harmful excipient and the safety of the majority of these excipients is not easily assessable based on information contained in the SPCs.

A European observational study described the extent of the administration of eight potentially harmful excipients (parabens, benzoates, benzalkonium chloride, saccharin sodium, sorbitol, propylene glycol, ethanol, polysorbate 80) in 89 third-level NICUs from 21 countries. Among 2,095 prescriptions (530 different products) administered to 726 neonates (477 preterm), the presence of potentially harmful excipients was found in 31% of prescriptions (142 products) and involved 456 neonates (63%). Parabens were used most frequently, followed by propylene glycol and benzoates. Major determinants resulted geographical area, gestational age and route of administration. In detail, variation of excipient administration reflected prescription behaviour among countries (for example the different proportion of vitamin prescriptions containing parabens or the non use of domperidone containing saccharin sodium in the East Europe); term neonates were less likely to receive parabens, benzoates and ethanol; enteral and topical formulations contained more frequently potentially harmful excipients. The authors concluded that a few commonly used medicines were responsible for a large part of potentially

Table 1. Summary of studies reporting exposure to potentially harmful excipients in NICUs.

Reference	Country/ area	Study period	Number of neonates	Number of prescriptions	Number of products	Number of products containing PHE (%)	Number of PHE (%)	Number of exposed neonates (%)
Nellis, 2015 [46]	Europe	1 day	726	2,095	530	142 (27%)	n.i.	456 (63%)
Garcia-Palop, 2016 [47]	Spain	n.i.	n.i.	n.i.	101	40 (40%)	n.i.	n.i.
Fister, 2015 [1]	Slovenia	1 month	48	n.i.	27	18 (66%)	29 (48%)	48 (100%)
Souza, 2014 [48]	Brazil	3 months	79	1,303	77	48 (62%)	57 (66%)	78 (99%)
Lass, 2012 [49]	Estonia	1 year	348	1,961	107	73 (68%)	47 (38%)	339 (97%)
Whittaker, 2009 [14]	UK	1 year	38	n.i.	n.i.	n.i.	7 (35%)	n.i.
Shehab, 2009 [30]	USA	1 year	1,190	170	n.i.	15	2	459 (39%)
Butler, 2007 [50]	UK	4 weeks	14	n.i.	29	16 (56%)	4	14 (100%)

In the last two rows of the penultimate column the lack of percentages is justified by the fact that the last two studies were focused only on 2 and 4 specific potentially harmful excipients.
PHE: potentially harmful excipient; n.i.: not indicated.

harmful excipients, therefore a substitution or a reformulation of products may spare many neonates from unnecessary exposure [46].

Similar data referred to a single unit/country have been reported by other authors.

Harmful excipients present in medicines given to neonates in Spain have been detected: 40% of drugs commonly used (101 different products), 32% of intravenous formulations and 62% of oral formulations contained at least one harmful excipient. As regards intravenous formulations, in 11% of cases more than one harmful excipient was present (sodium metabisulphite, ethanol, benzyl alcohol). Fifty percent of oral formulations contained two or more excipients, mainly parabens and sorbitol; 25% of intravenous formulations (diazepam, dopamine, sodium heparin and naloxone) and 19% of oral formulations (loperamide, carnitine, acyclovir) contained excipient amounts greater than the adult maximum when administered at doses recommended in neonates [47].

A prospective cross-sectional study was performed to determine the prevalence of excipient exposure in 48 newborns (9 preterm) admitted to the Department of Neonatology, Children's Hospital in Ljubljana (Slovenia) during a one-month period. Twenty-seven different pharmaceutical preparations were prescribed (78% industrially manufactured and 22% made at the hospital pharmacy), 12 for oral use and 10 by intravenous route. The most commonly administered medicines were antibiotics, antianaemics and vitamins, only one-third approved for use in neonates. Sixty excipients were present in 23/27 preparations, one-fourth classified as potentially harmful and 23% known to be harmful contained in 66% of preparations: all newborns received at least one potentially harmful excipient. Among excipients known to be harmful for neonates, ethanol, propylene glycol, saccharin sodium and benzoates were present in at least two pharmaceutical preparations of antibiotics (intravenous formulations), iron, vitamins and antifungals (oral formulations) [1].

The exposure to excipients among neonates hospitalized in the NICU of a public hospital in Brasilia (Brazil) was investigated during a three-month period. Seventy-nine newborns (64 preterm) received 1,303 prescriptions (77 different formulations related to 70 different active compounds). Of the 77 formulations examined, 48 (62%) contained excipients classified as potentially harmful. In total, 86 excipients were present, 66.2% categorized as potentially or known to be harmful. Almost all neonates (98.7%) were exposed at least to one excipient known to be harmful with differences among preterm and term newborns: preterms resulted at higher risk of exposure to polysorbate 80 and propylene glycol, while full-term neonates presented greater risks in relation to ethanol and methylparaben [48].

In a prospective cohort study, all medicines prescribed to 348 neonates (176 preterm) admitted to two Hospitals in Estonia (Tartu University Hospital and Tallinn Children's Hospital) during a 1-year period were recorded and analysed for their excipient content. A total of 123 excipients were found in 83% of 1,961 prescriptions (107 different medicines). 47/123 (38%) of these excipients were classified as potentially or known to be harmful (mostly parabens and sodium metabisulphite). Two thirds of parenteral products contained some potentially harmful excipients, while all of the rectal, topical, inhalatory and oral formulations contained at least one potentially harmful excipient. Almost all treated neonates (97%) were exposed at least to one potentially harmful excipient and 88% received one of the eight excipients known to be harmful for neonates: no differences were observed between preterm and term neonates. 57% of neonates were exposed to parabens, known to cause harm but used as preservatives in parenteral formulations of gentamicin. Oral suspensions of simeticone, the second commonly prescribed medicine given to 31% of neonates, contained two excipients known to be harmful (sodium benzoate and saccharin sodium) and three potentially harmful (sodium cyclamate, sorbic acid, colloidal anhydrous silica) [49].

Excipient exposure after use of oral liquid medications was retrospectively analysed in 38 preterm infants (BW < 1,500 g, GA ≤ 30 weeks) admitted to the NICU of University Hospital in Leicester (UK) between June 2005 and July 2006 with a diagnosis of chronic lung disease. More than 20 excipients were present in the examined formulations related to caffeine, furosemide, spironolactone, domperidone, dexamethasone, bendrofluazide, iron, vitamins: they included ethanol and propylene glycol associated to neurotoxicity (many infants exceeded the WHO acceptable daily intake limit for adults), but also benzoic acid, hydroxybenzoate, Ponceau 4R, sorbitol and saccharin [14].

Some authors [30] documented neonatal exposure to benzyl alcohol and propylene glycol present in 15 parenteral medications routinely

used in the NICU of the Mott Children's Hospital, University of Michigan. During the 1-year study period, 170 episodes of exposure to benzyl alcohol and propylene glycol regarding 459 neonates have been selected. Higher excipient doses were received with medications given by continuous infusion, compared to intermittent administration: in this subpopulation of neonates, cumulative excipient doses were respectively 21 and 180 times the acceptable daily intakes of these two drugs. Midazolam and lorazepam were involved in over two-thirds of exposures.

Other authors [50] analyzed the exposure to excipients potentially harmful in neonates admitted to a NICU (Princess Royal Maternity Unit, Glasgow Hospital, UK) over a period of 4 weeks. 56% of medicines given to 14 neonates (mean GA 31 weeks, mean BW 1,650 g) contained excipients of concern (ethanol, benzyl alcohol, benzoic acid, hydroxybenzoate, sodium metabisulphite). Some adverse reactions (ADRs) have been observed: gasping syndrome (benzyl alcohol), bronchospasm (sodium metabisulphite), bilirubin displacement (hydroxybenzoate). Three patients died.

The neonatal literature includes both short-term and long-term outcomes of exposure to excipients. There are well-documented, even if limited, case reports where the use of excipients in neonates has led to severe ADRs (**Tab. 2**).

A baby born at 24 weeks gestation and weighing 710 g developed a staphylococcal septicaemia initially treated with flucloxacillin and vancomycin. After the development of a red swollen knee and cheek, intravenous clindamycin was administered in place of vancomycin. After the third and fourth doses, the neonate suffered a profound desaturation and chest splinting that required resuscitation and suspension of the antibiotic. It was hypothesized the "gasping syndrome" due to the benzyl alcohol excipient present in the injectable formulation of clindamycin [9], as stated in the SPCs of the medicine and observed in preterm newborns treated i.v. with other drugs containing this preservative.

The same "gasping syndrome" was reported also in the 1980s by other authors in relation to the presence of benzyl alcohol in medications reconstituted with water containing this preservative and in bacteriostatic saline solutions used to flush catheters, a routine procedure at that time to maintain patency of cannulated arteries. In detail, sixteen premature infants weighing less than 1,500 grams developed a similar clinical syndrome characterized by the deterioration of multiple organs and died, as a probable result of the exposition to 0.9% benzyl alcohol contained in bacteriostatic water and NaCl used to flush periodically central intravascular catheters [7, 36]. Elevated levels of benzyl alcohol and its metabolites have been also detected in a critically ill newborn with RDS and intraventricular hemorrhage (IVH) (35 weeks' gestation), who received during the first 7 days of life large amounts of this toxic compound contained in a bacteriostatic saline solution from repeated umbilical arterial catheter flushes [51]. Other

Table 2. Case reports of suspected adverse reactions (ADRs) related to excipients.

Reference	Subject	Treatment	ADRs	Excipient	Outcome
Gershanik, 1982 [36]	10 preterm infants	flush saline solution	gasping syndrome	benzyl alcohol	death
Brown, 1982 [7]	6 preterm infants	flush saline solution	gasping syndrome	benzyl alcohol	death
Anderson, 1984 [51]	preterm infant (35 weeks)	flush saline solution	gasping syndrome	benzyl alcohol	recovery
Hiller, 1986 [52]	23 preterm infants	flush saline solution	severe IVH	benzyl alcohol	death
Jardine, 1989 [53]	15 preterm infants	flush saline solution	kernicterus	benzyl alcohol	death
Hall, 2004 [9]	neonate (24 weeks)	clindamycin	gasping syndrome	benzyl alcohol	recovery
Glasgow, 1983 [54]	preterm infant (27 weeks)	multivitamin prep.	hyperosmolality (ARF)	propylene glycol	recovery
MacDonald, 1987 [55]	127 preterm infants (< 1,500 g)	multivitamin prep.	seizures	propylene glycol	recovery (n = 96)/ death (n = 31)
Bove, 1985 [56]	8 preterm infants (< 1,200 g)	i.v. vit. E suppl.	renal dysfunction, hepatomegaly	polysorbate 20 and 80	death
Martone, 1986 [57]	14 preterm infants (≤ 1,250 g)	i.v. vit. E suppl.	renal dysfunction, hepatomegaly	polysorbate 20 and 80	death
Masi, 2009 [10]	newborn	amiodarone	cardiogenic shock	polysorbate 80, benzyl alcohol	recovery

ADRs: adverse reactions; IVH: intraventricular hemorrhage; ARF: acute renal failure.

authors examined cohorts of neonates before and after administration of solutions containing benzyl alcohol and underlined a possible association between the exposure to this excipient and a higher incidence of severe IVH and kernicterus in very low birth weight infants [52, 53].

A female infant (27-week gestation, body weight at birth 890 g) received parenteral nutrition from the 3rd day of life and aminophylline on the 9th day in association to respiratory support and phototherapy. On the 12th day, an unexplained acute renal failure was diagnosed. When parenteral nutrition was stopped for 48 h, the serum osmolality decreased. The reason of hyperosmolality was identified when a large amount of propylene glycol was detected in the urine: the main source of this substance was a multivitamin preparation (MVI-12) administered daily to the newborn with the parenteral nutrition solution. Since high amounts of propylene glycol have been detected in other infants treated with the same parenteral multivitamin complex, the multivitamin preparation was immediately removed from all parenteral nutrition solutions used in the nursery [54]. Other authors [55] reported an increased incidence of seizures, dose-related (33% vs 14%), in very low birth weight infants (BW < 1,500 grams) exposed to two different concentrations of propylene glycol, 300 mg and 3 g/day, contained in the same multivitamin preparation.

An unusual clinical syndrome was described in 1984, after a new i.v. vitamin E supplement (E-Ferol) containing high concentrations of polysorbate 20 and 80 was introduced in the market. This syndrome, characterized by thrombocytopenia, renal dysfunction, hepatomegaly and ascites, resulted fatal in 8 preterm newborns (BW < 1,200 g) who had received high doses of E-Ferol for a long period [56] and occurred in other 14 neonates who received more than 20 U/kg of E-Ferol [57]. Finally, a newborn presenting with supraventricular tachycardia developed cardiogenic shock and multiple organ dysfunction thirty minutes after receiving a high loading dose of intravenous amiodarone (30-minute infusion). Since the highest serum concentrations of amiodarone never exceeded the usual steady-state values, it has been hypothesized that the two excipients present in the i.v. commercial formulation, benzyl alcohol and polysorbate 80, could have precipitated the cardiogenic shock [10].

Conclusions

Because of their lack of pharmacological action, excipients have always been considered inert agents and for this reason underestimated. However, in the last years more interest grew on excipients because of safety concerns, particularly in the neonatal population where the immaturity of organ systems and metabolic pathways cannot always guarantee their efficient removal. The EMA has published a draft guideline on pharmaceutical development of medicines for paediatric use which contains a section on excipients. However, this guideline includes a useful approach to risk assessment but does not indicate how to handle uncertainty [4].

The use of excipients in neonatal formulations is driven by functional requirements, but should be justified through a risk-based assessment [58].

Some factors have to be considered in case of exposure to excipients: the safety profile of the excipient, how the medication containing the excipient is given (dosage and frequency, route of administration, duration of therapy), the existence of alternatives and the regulatory status. In addition, two other aspects need to be underlined. First, a "background level" of excipient exposure has to be taken into account in the first period of life, being different excipients present in products commonly prescribed to preterm infants such as iron, multivitamins and folic acid. Secondly, polypharmacy, relatively common in sick neonates, could lead to multiple sources of excipients, with risk of additive effects [14].

The maximum daily intake is of particular concern. The amount of excipients in drug formulations is rarely reported, making the evaluation of exposure and assessment of harmfulness of these substances in neonates very difficult. Moreover, the daily toxic threshold, if known, is referred to adults and an extrapolation is not always simple, due to the physiological characteristics of the neonatal population [2].

In order to minimize the risks, every excipient should be easily identified and explained as regards both its amount and function in the medicinal product. Moreover, there are clearly differences between excipient exposure among countries (differences in the choice of active compounds, in market availability and regulatory) that need to be accounted in research and regulatory actions.

At present, the EU and US Pediatric Formulation Initiatives are working together to create a database of Safety and Toxicity of Excipients for Paediatrics

(STEP project) to identify the gaps in the excipient knowledge and to provide a computerized source of information [59], while a new research (SEEN project) will contribute to reveal the current status of excipients in medicines administered to neonates [60]. Moreover, promising collaborative studies such as ESNEE project have been conducted in Europe with the aim to minimize the risks through actions such as excluding excipients associated with harm whenever possible or limiting their concentrations [19].

Neonatal exposure to potentially harmful excipients could be reduced without reformulation of existing medicines or introduction in the market of new products.

The use of preservative-free solutions in premature infants should be possible, for example, by packaging medications in single-dose vials without preservatives. In addition, in some situations it is possible a substitution of a medicine, since significant regional variations in administration of potentially harmful excipients exist in Europe and excipient-free products of the same active compound are available in the European market [46]. Some authors [49] underlined that in Estonia is available and used a formulation of gentamicin, one of the most commonly drugs used in neonates, containing well-known harmful excipients (parabens) while in Europe a paraben-free gentamicin product is also registered. This is in line with a Dutch study that reported in 22% of cases the existence of an alternative formulation to oral liquid medicines commonly used in the Netherlands containing potentially harmful excipients [17]. Recently, a 3-day survey was performed in 21 European countries (115 NICUs) to explore the possibility to avoid neonatal exposure to potentially harmful excipients through product substitution. 456 out of 726 neonates (63%) received 137 different medicines containing potentially harmful excipients (43% among 318 administered products). Substitution with potential harmful excipient-free products was possible in 50% of prescriptions and reduced the number of exposed neonates of 44% (from 456 to 257) [61].

In conclusion, as underlined also by some authors [5], for a safe use of excipients in neonates manufacturers should adopt best practices and regulatory agencies should provide guidance for industry, but overall prescribers need to be better informed on the quantitative composition of medicines and on potential adverse effects of excipients.

Declaration of interest

The Author declares that there is no conflict of interest.

References

1. Fister P, Uhr S, Karner A, Krzan M, Paro-Panjan D. The prevalence and pattern of pharmaceutical and excipient exposure in a neonatal unit in Slovenia. J Matern Fetal Neonatal Med. 2015;28(17):2053-61.
2. Fabiano V, Mameli C, Zuccotti GV. Paediatric pharmacology: remember the excipients. Pharmacol Res. 2011;63(5):362-5.
3. AAP. "Inactive" ingredients in pharmaceutical products: update (subject review). Pediatrics. 1997;99(2):268-78.
4. EMA. Guideline on Pharmaceutical Development of Medicines for Paediatric Use. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf, publication date: 2013, last access: March 2016.
5. Nahata MC. Safety of "inert" additives or excipients in paediatric medicines. Arch Dis Child Fetal Neonatal Ed. 2009;94(6):F392-3.
6. Turner MA, Duncan JC, Shah U, Metsvaht T, Varendi H, Nellis G, Lutsar I, Yakkundi S, McElnay JC, Pandya H, Mulla H, Vaconsin P, Storme T, Rieutord A, Nunn AJ. Risk assessment of neonatal excipient exposure: lessons from food safety and other areas. Adv Drug Deliv Rev. 2014;73:89-101.
7. Brown WI, Buist NRM, Gipson HT, Huston RH, Kennaway NG. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. Lancet. 1982;1(8283):1250-1.
8. Peleg O, Bar-Oz B, Arad I. Coma in a premature infant associated with the transdermal absorption of propylene glycol. Acta Paediatr. 1998;87(11):1195-6.
9. Hall C, Milligan D, Berrington J. Probable adverse reaction to a pharmaceutical excipient. Arch Dis Child Fetal Neonatal Ed. 2004;89(2):F184.
10. Masi S, Clety D, Clement S, Anslot C, Detaille T. Acute amiodarone toxicity due to an administration error: could excipient be responsible? Br J Clin Pharmacol. 2009;67(6):691-3.
11. Christiansen N. Ethanol exposure through medicines commonly used in paediatrics. Arch Dis Child Educ Pract Ed. 2015;100(2):101-4.
12. EMA, Committee for Medicinal Product for Human Use (CHMP). Guideline on excipients in the dossier for application for marketing authorization of a medicinal product 2007. CHMP/QWP/396951/2006.
13. EC. A guideline on Summary of Product Characteristics (SmPC). Available at: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf, publication date: 2009, last access: May 2017.
14. Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC. Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94(4):F236-44.

15. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Expert Opin Drug Saf. 2006;5(5):703-18.
16. EMA. Reflection paper: Formulations of choice for the paediatric population. Available at: http://www.ema.europa.eu/docs/eu_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf, publication date: 2006, last access: March 2016.
17. Van-Riet Nales DA, de Jager KE, Schobben AFAM, Egberts TCG, Rademaker CMA. The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol. 2011;72(3):465-73.
18. Kristensen HG. WHO guideline development of paediatric medicines: points to consider in pharmaceutical development. Int J Pharm. 2012;435(2):134-5.
19. Turner MA, Duncan J, Shah U, Metsvaht T, Varendi H, Nellis G, Lutsar I, Vaconsin P, Storme T, Rieutord A, Nunn AJ. European Study of neonatal exposure to excipients: an update. Int J Pharm. 2013;457(1):357-8.
20. Pughac S, Pughac IZ. Overdose in infant caused by over-the-counter cough medicine. South Med J. 2009;4:440-2.
21. Zuccotti GV, Fabiano V. safety issues with ethanol as an excipient in drugs intended for pediatric use. Expert Opin Drug Saf. 2011;10(4):499-502.
22. Pandya HC, Mulla H, Hubbard M, Cordell RL, Monks PS, Yakkundi S, McElnay JC, Nunn AJ, Turner MA on behalf of the ESNEE consortium. Essential medicines containing ethanol elevate blood acetaldehyde concentrations in neonates. Eur J Pediatr. 2016;175(6):841-7.
23. Jutley H, Christiansen N. Alcohol exposure in Neonatal Intensive Care patients. Proceedings 19th Neonatal Pediatric Pharmacist Group Conference, London, 8-10 November 2013.
24. FDA. Over-the-counter drug products intended for oral ingestion that contain ethanol. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=328&showFR=1, publication date: 2013, last access: April 2016.
25. EMA. Committee for Medicinal Products for Human Use (CHMP). Questions and answers on ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medical products for human use'. EMA/CHMP/507988/2013.
26. Propylene glycol. Hazardous Substances Databank (HSDB) [database on the Internet]. Bethesda (MD): National Library of Medicine US. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htlmgen?HSDB, last update: May 2004, last access: March 2016.
27. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. J Pediatr. 1978;93(3):515-6.
28. Speth PA, Vree TB, Neilen NF, de Mulder PH, Newell DR, Gore ME, de Pauw BE. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit. 1987;9(3):255-8.
29. FDA, FDA Drug Safety Communication. Serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm, publication date: 2011, last access April 2016.
30. Shehab N, Lewis CL, Streetman DD, Donn SM. Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. Pediatr Crit Care Med. 2009;10(2):256-9.
31. 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(2):112-4.
32. Miszkiel KA, Beasley R, Rafferty P, Holgate ST. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. Br J Clin Pharmacol. 1988;25(2):157-63.
33. LeBel M, Ferron L, Masson M, Pichette J, Carrier C. Benzyl alcohol metabolism and elimination in neonates. Dev Pharmacol Ther. 1988;11(6):347-56.
34. Haslund-Krog S, Mathiasen R, Christensen HR, Holst H. The impact of legislation on drug substances used off-label in paediatric wards-a nationwide study. Eur J Clin Pharmacol. 2014;70(4):445-52.
35. AAP. Committee on Fetus and Newborn, Section on Surgery, Anesthesiology and Pain Medicine; Canadian Pediatric Society, Fetus and Newborn Committee. Batton DG, Barrington KJ, Wallman C. Prevention and management of pain in the neonate: an update. Pediatrics. 2006;118(5):2231-41.
36. Gershanik J, Boecler B, Hensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med. 1982;307(22):1384-8.
37. European Food Safety Authority. EFSA advises on the safety of paraben usage in food. Available at: www.efsa.europa.eu/en/press/news/afc040929, publication date: 2004, last access: May 2017.
38. Yakkundi S, Mulla H, Pandya H, Turner MA, McElnay J. Quantitative analysis of methyl and propyl parabens in neonatal DBS using LC-MS/MS. Bioanalysis. 2016;8(11):1173-82.
39. Koepke JW, Christopher KL, Chai H, Selner JC. Dose-dependent bronchospasm from sulfites in isoetharine. JAMA. 1984;251(22):2982-3.
40. Turner MA, Baines P. Which inotrope and when in neonatal and paediatric intensive care? Arch Dis Child Educ Pract Ed. 2011;96(6):216-22.
41. Duro D, Rising R, Cedillo M, Lifschitz F. Association between infantile colic and carbohydrate malabsorption from fruit juices in infancy. Pediatrics. 2002;109(5):797-805.
42. Aires CP, Tabchoury CP, Del Bel Cury AA, Koo H, Cury JA. Effect of sucrose concentration on dental biofilm formed in situ and on enamel demineralization. Caries Res. 2006;40(1):28-32.

43. Stegink LD, Filer LJ, Bell EF, Ziegler EE, Tephly TR, Krause WL. Repeated ingestion of aspartame-sweetened beverages: further observations in individuals heterozygous for phenylketonuria. Metabolism. 1990;39(10):1076-81.
44. Tollefson L, Barnard RJ. An analysis of FDA passive surveillance reports of seizures associated with consumption of aspartame. J Am Diet Assoc. 1992;92(5):598-601.
45. Walker AM, Dreyer NA, Friedlander E, Loughlin J, Rothman KJ, Kohn HI. An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. Am J Public Health. 1982;72(4):376-81.
46. Nellis G, Metsvaht T, Varendi H, Toompere K, Lass J, Mesek I, Nunn AJ, Turner MA, Lutsar I, on behalf of the ESNEE consortium. Potentially harmful excipients in neonatal medicines: a pan-European observational study. Arch Dis Child. 2015;100(7):694-9.
47. Garcia-Palop B, Movilla Polanco E, Canete Ramirez C, Cabanas Poy MJ. Harmful excipients in medicines for neonates in Spain. Int J Clin Pharm. 2016;38(2):238-42.
48. Souza A, Santos D, Fonseca S, Medeiros M, Batista L, Turner M, Coelho H. Toxic excipients in medications for neonates in Brazil. Eur J Pediatr. 2014;173(7):935-45.
49. Lass J, Naelapaa K, Shah U, Kaar R, Varendi H, Turner MA, Lutsar I. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. BMC Pediatr. 2012;12:136.
50. Butler E, Grant J. Identify and quantify exposure to excipients in neonates. [Abstract]. Paediatr Child Health. 2007;17:10.
51. Anderson CW, Ng KJ, Andresen B, Cordero L. Benzyl alcohol poisoning in a premature newborn infant. Am J Obstet Gynecol. 1984;148(3):344-6.
52. Hiller JL, Benda GI, Rahatzad M, Allen JR, Culver DH, Carlson CV, Reynolds JW. Benzyl alcohol toxicity: impact on mortality and intraventricular haemorrhage among very low birth weight infants. Pediatrics. 1986;77(4):500-6.
53. Jardine DS, Rogers K. Relationship of benzyl alcohol to kernicterus, intraventricular haemorrhage and mortality in preterm infants. Pediatrics. 1989;83(2):153-60.
54. Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP. Hyperosmolality in small infants due to propylene glycol. Pediatrics. 1983;72(3):353-5.
55. MacDonald MG, Getson PR, Glasgow AM, Miller MK, Boeckx RL, Johnson EL. Propylene glycol: increased incidence of seizures in low birth weight infants. Pediatrics. 1987;79(4): 622-5.
56. Bove KE, Kosmetatos N, Wedig KE, Frank DJ, Whitlatch S, Saldivar V, Haas J, Bodenstein C, Balistreri WF. Vasculopathic hepatotoxicity associated with E-Ferol syndrome in low-birth-weight infants. JAMA. 1985;254(17):2422-30.
57. Martone WJ, Williams WW, Mortensen ML, Gaynes RP, White JW, Lorch V, Murphy MD, Sinha SN, Frank DJ, Kosmetatos N, Bodenstein CJ, Roberts RJ. Illness with fatalities in premature infants: association with an intravenous vitamin E preparation, E-Ferol. Pediatrics. 1986;78(4):591-600.
58. Sam T, Ernest TB, Walsh J, Williams JL, on behalf of the European Paediatric Formulation Initiative (EuPHI). A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms – An application for paediatric dosage form selection. Int J Pharm. 2012;435:115-23.
59. Salunke S, Giacoia G, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1-A need assessment study. Int J Pharm. 2012;435(2):101-11.
60. Valeur KS, Hertel SA, Lundstrom KE, Holst H. Safe excipient exposure in neonates and small children-protocol for the SEEN project. Dan Med J. 2017;64(2):A5324.
61. Nellis G, Metsvaht T, Varendi H, Lass J, Duncan J, Nunn AJ, Turner MA, Lutsar I. Product substitution as a way forward in avoiding potentially harmful excipients in neonates. Pediatr Drugs. 2016;18(3):221-30.