The prevalence and pattern of pharmaceutical and excipient exposure in a neonatal unit in Slovenia

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Abstract

Objective: Because of the restraints on conducting studies on pharmaceutical use in sick newborns, many drugs are used off-label in this population. Moreover, industrially manufactured pharmaceuticals may contain different excipients, which may be either untested or not licensed for use in neonates. The aim of our study was to determine the prevalence and pattern of pharmaceutical and excipient exposure in newborns hospitalized at the Department of Neonatology, Ljubljana, Slovenia.

Methods: A longitudinal prospective cross-sectional study was performed during a one-month period and included all hospitalized neonates. Route of administration, site of action, type of manufacture, licensing status, type and concentrations of excipients for all pharmaceuticals given to the neonates were determined.

Results: Twenty seven different pharmaceutical preparations were prescribed to a total of 48 hospitalized newborns. In most cases, newborns were prescribed various pharmaceuticals that were not approved for use in this population. Newborns were exposed to 60 different excipients in industrially manufactured pharmaceutical preparations. More than half of the received pharmaceuticals contained potentially harmful and harmful excipients.

Conclusions: Two-thirds of pharmaceutical preparations for neonates were used off-label. Newborns receive more auxiliary substances, which may be unsuitable for this age group and may even be toxic to them, via industrially manufactured pharmaceuticals.

Keywords

Additives, newborn, off-label use of medicinal preparations

History

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Introduction

Due to the immaturity of their organ systems and metabolic pathways, newborns are an especially vulnerable population. The effect of the active ingredient or excipients in pharmaceutical preparations can be substantially different in neonates than in infants, children and adults. The prescription of pharmaceutical preparations to newborns is usually empiric due to lack of clinical studies in this population [1]. It is estimated that only one-third to one-fourth of pharmaceutical preparations that are prescribed to neonates are adequately tested in this population. Therefore, the practice of prescribing unapproved pharmaceuticals in neonatology is very common [2]. According to a report of the European Medicine Agency (EMA), up to 90% of the prescribed pharmaceutical preparations used in premature newborns are either unlicensed or used in an off-label manner [3,4]. Moreover, industrially manufactured pharmaceutical preparations in particular contain many excipients within one pharmaceutical preparation that have not been either tested or licensed for use in neonates.

Excipients are inactive ingredients of pharmaceutical preparations that are added to medicines to ensure properties such as solubility and bioavailability, as well as to promote stability of the final dosage form. They are supposed to be pharmacologically inactive [5,6]. However, there have been occasional reports that some of the excipients used in pharmaceutical preparations have caused various and, in some cases, serious adverse effects in neonates [7]. According to a policy statement by the American Academy of Pediatrics, the kind of excipient in a given pharmaceutical preparation should be labeled [7–9].

In order to evaluate, the exposure of newborns to drugs and excipients in prescribed pharmaceutical preparations, our study analyzed pharmaceuticals with regard to the usage, license, type of manufacture (industrially produced or compounding preparations), and type, number and potential toxicity of excipients.

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Materials and methods
We performed a cross-sectional, pilot, prospective study from 1 to 31 March 2011 at the Clinical Department of Neonatology, Children’s Hospital, University Medical Centre Ljubljana, Slovenia. For each hospitalized newborn we recorded: sex, gestational age, birth weight, weight at admission and the indication for admission, as well as the list of pharmaceutical preparations prescribed together with route of administration, site and mechanism of action, and type of manufacture. Each pharmaceutical preparation was classified into on- or off-label for use during the neonatal period. Off-label categories were given if the preparation was not approved use during the neonatal period due to age, weight, lack of pediatric clinical data, contraindication, route of administration or lack of suitable formulation. For each pharmaceutical product the dosage or concentrations of excipients in the preparation were collected using the summary of product characteristics (SPC) in the marketing authorization and compounding formulations.

The types of excipients were first classified according to their function in the pharmaceutical preparation, then the excipients were classified according to the available safety data, as proposed by Lass et al. and Turner et al. [6,10].

Results
During a one-month period, a total of 48 newborns (25 males and 23 females) were hospitalized in our department. Thirty-nine (81%) were mature and 9 (19%) were immature with an average birth weight of 3150 g (min 1100 g, max 4720 g, SD 760 g) and an average weight at admission of 3270 g (min 2300 g, max 4875 g, SD 567 g). Twenty-seven different pharmaceutical preparations were prescribed to the hospitalized newborns (Table 1). The indications for admission were cardiovascular and neurological diseases, urogenital and respiratory tract infections, jaundice, hypoglycemia, prematurity and small for gestational age.

Almost half of the pharmaceutical preparations were prescribed for oral use (12/27, 44%), 10/27 for intravenous, one for intranasal and one for intramuscular use. The majority of the prescribed pharmaceutical preparations were pharmaceuticals with systemic (24/27, 89%) rather than local effects (3/27, 11%). Almost three-quarters of the prescribed pharmaceutical preparations were industrially manufactured (21/27, 78%) and the rest were compounding preparations, made at the hospital pharmacy. The majority of the pharmaceuticals administered were antibiotics, followed by pharmaceuticals to treat anemia and vitamins. The minority represented bronchodilators (pharmaceuticals for obstructive pulmonary diseases), hypnotics, sedatives, topical antimycotics, thyroid hormones, diuretics, opiates and decongestives (S1). Only one-third of the prescribed pharmaceutical preparations were approved for use in newborns, which means that they were used in accordance with the SPC. Almost two-thirds of the prescribed pharmaceutical preparations were not approved for neonatal use and thus used off-label. In most cases, newborns were prescribed pharmaceutical preparations that were classified as not approved for use in newborn populations due to lack of licensing for age (11/17, 65%) or were disapproved for use in children due to lack of pediatric clinical data (7/17, 41%; Table 1). Two of the prescribed pharmaceuticals used were not approved for neonates due to weight restrictions and one was not approved due to route of administration. All the compounding preparations were used off-label due to lack of drug formulations suitable for newborns. In Supplemental Digital Content (S2), we present the on-label use of the prescribed pharmaceutical preparations that were used off-label in our study.

In the prescribed pharmaceutical preparations, a total of 60 excipients were present, classified into 21 groups according to their function in the pharmaceuticals (Table 2). In total 23/27 pharmaceutical preparations contained at least one excipient. According to the available safety data, one-fourth of excipients in the prescribed pharmaceuticals were classified as potentially harmful (15/60, 25%) and all the newborns received at least one pharmaceutical preparation with a potentially harmful excipient (Table 3) [11–15]. Moreover, slightly under one-fourth of the excipients (14/60, 23%) added to pharmaceutical preparations were known to be harmful in neonates and an additional two excipients were known to be harmful to older age groups [6]. Taken together, one-fourth of all the excipients that newborns were receiving were known to be harmful (16/60, 26%) and they were contained in almost half of the received pharmaceuticals (13/27, 48%). Altogether, two-third of the prescribed pharmaceutical preparations contained potentially harmful and harmful excipients (18/27, 63%)

Table 1. Off-label categories of the prescribed pharmaceutical preparations.

| Off-label category | Pharmaceutical preparation |
|--------------------|---------------------------|
| Age                | AD3 6000 i.e./2000 i.e. in 1 ml, oral drops, emulsion; betrion 20 mg/g ointment; ceclor 125 mg/5 ml granules for oral suspension; daktarin 20 mg/g oromucosal gel; edemid 10 mg/ml solution for injection (for premature neonates); fucidin 20 mg/g ointment; gobemicina 500 mg powder for solution for injection or infusion; operil 0.25 mg/ml nasal drops for children, solution; plivit D3 4000 i.e./ml, oral drops, solution; zinnat 125 mg/5 ml granules for oral suspension |
| Weight             | Eprex 1000 IE/0.5 ml solution for injection in pre-filled syringe; zinnat 125 mg/5 ml granules for oral suspension |
| Lack of pediatric clinical data | Zinnat 125 mg/5 ml granules for oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml syrup; levotiroxine 25 mcg oral powder; morphine hydrochloride 0.4 mg/ml oral solution for children; theophylline 2.5 mg/ml oral suspension; α-tocopherol (vitamin E) 100 mg oral powder |
| Contraindication   | Daktarin 20 mg/g oromucosal gel |
| Route of administration | Morphine hydrochloride 0.4 mg/ml oral solution for children |
| Lack of suitable formulation | Caffeine citrate 20 mg/ml syrup; Chloral hydrate 40 mg/ml syrup; levotiroxine 25 mcg oral powder; morphine hydrochloride 0.4 mg/ml oral solution for children; theophylline 2.5 mg/ml oral suspension; α-tocopherol (vitamin E) 100 mg oral powder |

Table 2. Description of pharmaceutical preparations.

| Pharmaceutical preparation | Excipient |
|----------------------------|-----------|
| AD3 6000 i.e./2000 i.e. in 1 ml, oral drops, emulsion | -tocopherol (vitamin E) 100 mg oral powder |
| betrion 20 mg/g ointment | -tocopherol (vitamin E) 100 mg oral powder |
| ceclor 125 mg/5 ml granules for oral suspension | -tocopherol (vitamin E) 100 mg oral powder |
| daktarin 20 mg/g oromucosal gel | -tocopherol (vitamin E) 100 mg oral powder |
| edemid 10 mg/ml solution for injection (for premature neonates) | -tocopherol (vitamin E) 100 mg oral powder |
| fucidin 20 mg/g ointment | -tocopherol (vitamin E) 100 mg oral powder |
| gobemicina 500 mg powder for solution for injection or infusion | -tocopherol (vitamin E) 100 mg oral powder |
| operil 0.25 mg/ml nasal drops for children, solution | -tocopherol (vitamin E) 100 mg oral powder |
| plivit D3 4000 i.e./ml, oral drops, solution | -tocopherol (vitamin E) 100 mg oral powder |
| zinnat 125 mg/5 ml granules for oral suspension | -tocopherol (vitamin E) 100 mg oral powder |
| Eprex 1000 IE/0.5 ml solution for injection in pre-filled syringe | -tocopherol (vitamin E) 100 mg oral powder |
| Zinnat 125 mg/5 ml granules for oral suspension | -tocopherol (vitamin E) 100 mg oral powder |
| Caffeine citrate 20 mg/ml syrup | -tocopherol (vitamin E) 100 mg oral powder |
| Chloral hydrate 40 mg/ml syrup | -tocopherol (vitamin E) 100 mg oral powder |
| Levotiroxine 25 mcg oral powder | -tocopherol (vitamin E) 100 mg oral powder |
| Morphine hydrochloride 0.4 mg/ml oral solution for children | -tocopherol (vitamin E) 100 mg oral powder |
| Theophylline 2.5 mg/ml oral suspension | -tocopherol (vitamin E) 100 mg oral powder |
| α-Tocopherol (vitamin E) 100 mg oral powder | -tocopherol (vitamin E) 100 mg oral powder |
**Table 2. Types of excipients according their function in the pharmaceutical preparation.**

| Types of excipients | Identified excipients in the pharmaceutical preparation given to the studied neonates |
|---------------------|--------------------------------------------------------------------------------------|
| Antifoaming agent   | Polydimethylsiloxane (dimethicone)                                                  |
| Antioxidants        | Butylhydroxytoluene (BHT) (E321); citric acid (E330); sodium metabisulfite (E 223); α-tocopherol |
| Binders             | Gelatin (E443); maize starch; microcrystalline cellulose and carmelllose sodium; povidone K30; starch, pregelatinised; sucrose |
| Buffering agent     | Calcium sulfate (E516); citric acid (E330); disodium edentate; disodium phosphate, anhydrous; disodium phosphate, dehydrate; glycine; hydrochloric acid, concentrated (E 507); sodium chloride; sodium hydroxide (E524) sodium phosphate |
| Coatings            | Methylcellulose (E461)                                                              |
| Colors              | Erythrosine (E127)                                                                 |
| Cofreeze-dried excipient in injectable formulation | Glycine; histidine; mannitol |
| Diluents            | Water for injections; water, purified                                               |
| Disintegrants       | Methylcellulose (E461), microcrystalline cellulose and carmelllose sodium; povidone K30, starch, pregelatinized |
| Emulsifying agent   | Polysorbate 20                                                                     |
| Fillers             | Lactose monohydrate; sucrose                                                       |
| Flavors             | Aromas: cocoa, mixed fruit, orange, sour cherry, strawberry; syrup rubi              |
| Granulation aid     | Sucrose                                                                             |
| Lubricants          | Magnesium stearate; maize starch; silicic acid; sodium lauryl sulphate              |
| Ointment base       | Lanolin (emulsifying agent); paraffin, liquid; paraffin, white soft (ointment base); macrogol 3350 (ointment base); polysorbate 20 (emulsifying); cetyl alcohol (emulsifying agent); glycerol (E422) (emolient) |
| Preservatives       | Benzalkonium chloride; citric acid (E330); glycerol (E422); methylparaben; methyl para-hydroxybenzoate (E218); potassium sorbate; propyl paraben; propyl para-hydroxybenzoate (E216); propylene glycol (E1520); sodium benzoate (E211); sodium methyl para-hydroxybenzoate (E219); sodium propyl para-hydroxybenzoate (E217); sodium metabisulfite (E223) |
| Suspending and gelling agents | Carboxymethylcellulose sodium (E466); carrageenan (E407); microcrystalline cellulose; povidone K30; xanthan gum (E415) |
| Solubilizing agent  | Macrogolglycerol hydroxystearate; polysorbate 80 (E433); stearic acid              |
| Solvents, co-solvents | Ethanol (96%); glycerol (E422); macrogol 400; mannitol; propylene glycol (E1520) |
| Stabilizing agent   | Disodium edetate; disodium phosphate, anhydrous; disodium phosphate, dihydrate; sorbitol (E420) |
| Sweeteners          | Acesulphame potassium; aspartame (E951); glycerol (E422); saccharin sodium; sorbitol (E420); sucrose |

66%). Finally, less than half of the prescribed excipients were classified in the “potentially safe” category (29/60, 48%, Table 3).

All newborns received at least one of the pharmaceutical preparations containing an excipient known to be harmful to neonates. The median number of excipients known to be harmful for neonates was one per pharmaceutical preparation. Two prescribed pharmaceutical preparations contained four of the known harmful excipients and three of them contained three such excipients. Of the excipients known to be harmful to neonates, ethanol was contained in three pharmaceutical preparations and propylene glycol in two. None of our neonates were exposed to benzyl alcohol. Regarding sweeteners, acesulfame potassium and aspartame were present in one pharmaceutical preparation, saccharin sodium was present in three pharmaceutical preparations, glycerol and sorbitol were present in five different pharmaceuticals, and sucrose was present in six.

**Discussion**

The main goal of EU Decree on pediatric drugs according to which EMA issued a reflection paper [16] is to assure that the medical products intended for use in children are proven safe and effective [17]. However, researchers conducting clinical research in the pediatric population, among which the group of mature and immature newborns is particularly vulnerable, encounter specific problems, such as ethical dilemmas, technical concerns due to the limited quantities of material to be sampled, difficulties in assessing pharmacodynamic effects and the need to develop suitable pharmaceutical formulations [18]. The result is that only 25–30% of the pharmaceutical preparations used in neonates are appropriately clinically tested for this age group [2–4]. In our study, only 37% of the 27 different pharmaceutical preparations had been used in accordance with the approved indication (on-label) for both mature and premature neonates, while the majority (63%) of the prescribed pharmaceuticals were used off-label due to either age and/or weight restrictions, lack of pediatric clinical data, contraindication, route of administration or lack of suitable formulation, although all preparations were licensed for the specific medical condition under treatment.

A similar study was performed in the neonatal department of the University Hospital of Bari in Italy. The authors reported that in a two-month period 34 newborns were prescribed 61 different pharmaceutical preparations. Of these, 88% were licensed and 12% were not. Only 37% of the licensed pharmaceutical preparations were used following the terms of the marketing authorization, which is comparable to our results; 27% of the prescribed pharmaceuticals were licensed for pediatric use, but were used off-label with the same regard as in our study, and 23% of the pharmaceutical preparations were not licensed for pediatric use at all [19].

The results of our study show that newborns are prescribed 78% industrially manufactured and 22% compounding preparations, which was contrary to our expectations. When there are no suitable formulations of specific pharmaceuticals on the market, newborns are often treated with compounding preparations. In two of the few available studies, which were conducted in the pediatric departments of Medical Centres in Netherlands, pharmaceutical preparations were prescribed to
| Category | Identified excipients in the pharmaceutical preparations given to the studied neonates | Pharmaceutical preparations containing the excipient |
|----------|--------------------------------------------------------------------------------------|-----------------------------------------------------|
| Potentially safe | Aromas (orange, strawberry, cocoa, sour cherry, mixed fruit, syrup rubi) | AD: 6000 i.e./2000 i.e. oral drops; ceclor 125 mg/5 ml granules for oral suspension; daktarin 20 mg/g oromucosal gel; legofer 40 mg/15 ml oral solution; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| | Calcium sulfate (E516) | Thymyline 2.5 mg/ml oral suspension |
| | Carboxymethylcellulose sodium | Thymyline 2.5 mg/ml oral suspension |
| | Citric acid (E330) | 3 Plivot D 4000 i.e./ml oral drops; solution; caffeine citrate 20 mg/ml syrup; carboxymethylcellulose sodium (E466) 1 Theophylline 2.5 mg/ml oral suspension |
| | Citral (E132) | 2 AD: 6000 i.e./2000 i.e. oral drops; ceclor 125 mg/5 ml granules for oral suspension; daktarin 20 mg/g oromucosal gel; legofer 40 mg/15 ml oral solution; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| | Glycerol (E422) | 3 4000 i.e./2000 i.e./ml oral drops; daktarin 20 mg/g oromucosal gel; theophylline 2.5 mg/ml oral suspension |
| | Histidine | 1 Synagis 50 mg powder and solvent for solution for injection |
| | Hydrochloric acid, concentrated (E507) | 3 Dormicum 1 mg/ml solution for injection or infusion; edemid 10 mg/ml solution for injection; morphine hydrochloride 0.4 mg/ml solution for injection; zinam 25 mg/5 ml oral suspension |
| | Lactose monohydrate | 2 Levothyroxine 25 mg oral powder; a-tocopherol (vitamin E) 100 mg oral powder |
| | Lecithin | 1 Fucidin 20 mg/g ointment |
| | Magnesium stearate (E572) | 1 Levothyroxine 25 mg oral powder; microcrystalline cellulose and carmellose sodium 2 Ceclor 125 mg/5 ml granules for oral suspension |
| | Paraffin, liquid | 1 Zinnat 125 mg/5 ml granules for oral suspension |
| | Polyethylene glycol 400 | 1 Ferrum Lek 50 mg/5 ml syrup; daktarin 20 mg/g oromucosal gel; legofer 40 mg/15 ml oral suspension; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| | Polyethylene glycol 4000 | 3 Ferrum Lek 50 mg/5 ml syrup; legofer 40 mg/15 ml oral suspension; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| | Sorbitol (E420), Sorbitol, liquid (non crystallizing) | 3 Ferrum Lek 50 mg/5 ml syrup; legofer 40 mg/15 ml oral suspension; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| | Stearic acid | 1 Statin 125 mg/5 ml granules for oral suspension |
| | Stearic acid | 6 AD: 6000 i.e./2000 i.e. oral drops; ceclor 125 mg/5 ml granules for oral suspension; Ferrum Lek 50 mg/5 ml syrup; daktarin 20 mg/g oromucosal gel; legofer 40 mg/15 ml oral solution; zinam 25 mg/5 ml granules for oral suspension; chloral hydrate 40 mg/ml oral suspension; caffeine citrate 20 mg/ml syrup; chloral hydrate 40 mg/ml oral suspension; theophylline 2.5 mg/ml oral suspension |
| Category                                  | Identified excipients in the pharmaceutical preparations given to the studied neonates                                                                 | Safety concern [7,8,11,12]                                                                 | Number of pharmaceutical preparations containing the excipient | Pharmaceutical preparations containing the excipient                                                                 |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Potentially harmful                      | Acesulfame potassium                                                                                                | Cariogenic, potentiates glucose-induced insulin release                                        | 1                                                            | Zinnat 125 mg/5 ml granules for oral suspension                                                                    |
|                                          | Aspartame (E951)                                                                                                  | A source of phenylalanine; gastrointestinal signs and dermatological signs                      | 1                                                            | Zinnat 125 mg/5 ml granules for oral suspension                                                                    |
|                                          | Butylhydroxytoluene (E321)                                                                                         | Local skin reactions (e.g., contact dermatitis) or irritation to the mucous membranes           | 2                                                            | Fucidin 20 mg/g ointment; plivit D3 4000 i.e./ml oral drops; cephalosporin 20 mg/g oromucosal gel; Ferrum Lek 50 mg/5 ml syrup | Eprex 1000 IE/0.5 ml solution for injection in pre-filled syringe; edemid 10 mg/ml solution for injection; garamycin 80 mg/2 ml solution for injection or infusion; gentamicin Krka 40 mg/ml solution for injection or infusion; synagis 50 mg powder and solvent for solution for injection; morphine hydrochloride 0.4 mg/ml oral solution for children |
|                                          | Carrageenan                                                                                                       | Induces inflammatory responses; may be associated with cancer in the intestinal tract           | 1                                                            | Theophylline 2.5 mg/ml oral suspension                                                                            |
|                                          | Disodium edetate                                                                                                | Disodium edetate, trisodium edetate, and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period of time, or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth; local inflammatory reactions | 3                                                            | Garamycin 80 mg/2 ml solution for injection or infusion; gentamicin Krka 40 mg/ml solution for injection or infusion; morphine hydrochloride 0.4 mg/ml oral solution for children |
|                                          | Disodium phosphate, anhydrous, disodium phosphate, dihydrate                                                     | Mild saline laxatives; gastrointestinal disturbances including diarrhea, nausea and vomiting    | 2                                                            | Eprex 1000 IE/0.5 ml solution for injection in pre-filled syringe; operil 0.25 mg/ml nasal drops for children, solution |
|                                          | Erythrosine (color E127)                                                                                          | Acute bronchospasm, nonimmunologic urticaria, eosinophilia and angioedema; dermatologic reactions, including photosensitivity, erythroderma and desquamation, concerns about carcinogenicity; might have an adverse effect on the thyroid gland | 1                                                            | Cefaclor 125 mg/5 ml granules for oral suspension                                                                  |
| Category | Identified excipients in the pharmaceutical preparations given to the studied neonates | Safety concern [7,8,11,12] | Number of pharmaceutical preparations containing the excipient | Pharmaceutical preparations containing the excipient |
|----------|-------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------|---------------------------------------------------|
| Gelatin (E443) | Local irritation; hypersensitivity reactions, including serious anaphylactoid reactions | 2 | Levothyroxine 25 mcg oral powder; α-tocopherol (vitamin E) 100 mg oral powder | |
| Glycine | Systemic absorption of glycine irrigation solutions can lead to disturbances of fluid and electrolyte balance and cardiovascular and pulmonary disorders | 2 | Epirex 1000 IE/0.5 ml solution for injection in pre-filled syringe; synagis 50 mg powder and solvent for solution for injection | |
| Macrogolglycerol hydroxystearate | Hypersensitivity reactions, hyperosmolarity and metabolic acidosis | 2 | AD3 6000 i.e./2000 i.e./ml oral drops; plivit D3 4000 i.e./ml oral drops, solution | |
| Macrogol 3350, macrogol 400 | Stinging when used topically, especially on mucous membranes, and have been associated with hypersensitivity reactions such as urticaria; abdominal cramps, vomiting and anal irritation may also occur and there have been rare reports of possible hypersensitivity reactions | 2 | Betrin 20 mg/g ointment; plivit D3 4000 i.e./ml oral drops, solution | |
| Povidone K30 | Hypersensitivity | 1 | Zinnat 125 mg/5 ml granules for oral suspension | |
| Sodium lauryl sulfate | Acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomach | 1 | Cezol 125 mg/5 ml granules for oral suspension | |
| Sodium phosphate | Mild saline laxatives; gastrointestinal disturbances including diarrhea, nausea and vomiting | 1 | Theophylline 2.5 mg/ml oral suspension | |

| Category | Identified excipients in the pharmaceutical preparation given to the studied neonates | Safety concern [6–8,11,12] | Number of pharmaceutical preparations containing the excipient | Pharmaceutical preparations containing the excipient |
|----------|-------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------|---------------------------------------------------|
| Known to be harmful to neonates | Benzalkonium chloride | Eye irritation and hypersensitivity; bronchoconstriction | 1 | Operil 0.25 mg/ml nasal drops for children, solution | |
| | Ethanol (96%) | CNS depression – muscle incoordination, visual impairment Chronic toxicity Negative syner-gic effect on CNS when associated with propylene glycol | 3 | AD3 6000 i.e./2000 i.e./ml oral drops; daktarin 20 mg/g oromucosal gel; Ferrum Lek 50 mg/5 ml syrup | |
| | Methylparahydroxybenzoate (E218) | Hypersensitivity reactions, harmful stimulation of the CNS and convulsions | 4 | Ferrum Lek 50 mg/5 ml syrup; garamycin 80 mg/2 ml solution for injection or infusion; gentamicin Krka 40 mg/ml solution for injection or infusion; plivit D3 4000 i.e./ml oral drops, solution. | |
| | Methylparaben | Hypersensitivity reactions, generally of the delayed type and appearing as contact dermatitis | 1 | Theophylline 2.5 mg/ml oral suspension | |
| | Saccharin sodium | Urticaria with pruritus followed by eczema, photosensitivity and prurigo; wheezing, nausea, diarrhea, tongue blisters, tachycardia, fixed eruptions, polyuria and sensory neuropathy; irritability, hypertonia, insomnia, opisthotonus and strabismus | 3 | AD3 6000 i.e./2000 i.e./ml oral drops; daktarin 20 mg/g oromucosal gel; legofer 40 mg/15 ml oral solution | |
| Excipient | Identified in the pharmaceutical preparation given to the studied neonates | Safety concern [7,8,11,12] | Number of pharmaceutical preparations containing the excipient | Pharmaceutical preparations containing the excipient |
|-----------|-------------------------------------------------|-----------------------------|-------------------------------------------------|--------------------------------------------------|
| **Known to be harmful to older age groups** | | | | |
| Sodium metabisulfite (E223) | Hypersensitivity-type reactions, including bronchospasm and anaphylaxis; wheezing and chest tightness in known reactive airway disease | 2 | Garamycin 80 mg/2 ml solution for injection or infusion; gentamicin Krka 40 mg/ml solution for injection or infusion |
| Cetyl alcohol | Allergic delayed-type hypersensitivity reactions in patients with stasis dermatitis, cross-sensitization with cetostearyl alcohol, lanolin and stearyl alcohol; local skin reactions (e.g. contact dermatitis) | 1 | Fucidin 20 mg/g ointment |
children aged from 0 to 17 years. Again, only one-third of the prescribed pharmaceutical preparations were licensed for use in children and one-third of the prescribed pharmaceuticals (760/2139) were produced or processed in the hospital pharmacy [20,21]. In the Dutch hospital, children were prescribed more compounding preparations than in our study. Unfortunately, our results are not fully comparable to the results of the Dutch study as they enrolled patients aged from a few days old to 17 years old.

Another aim of our study was to analyze the potential exposure of sick neonates to excipients in pharmaceutical preparations. One-fourth of the prescribed excipients are classified as potentially harmful and another quarter are classified as known to be harmful to neonates. Altogether, more than half of the received pharmaceuticals contained potentially harmful and harmful excipients. We are aware of only one other such study, from Estonia, where they describe that more than one-third of excipients in pharmaceutical preparations are potentially harmful to the neonatal population. Similarly, they report that two-thirds of the pharmaceutical preparations contained excipients potentially harmful to their study group [6].

Another study, conducted at the The Leicester Neonatal Service in the UK has revealed that infants diagnosed with chronic lung disease (1500 g, gestational age less than 30 weeks) were exposed to at least 20 different excipients in pharmaceutical preparations, such as sorbitol, ethanol and propylene glycol, in quantities that were larger than those recommended for use in adults [22]. Namely, sorbitol in large quantities causes osmotic diarrhea and is hepatotoxic, while ethanol and propylene glycol have been shown to be neurotoxic [23,24]. Neonates in our study were also exposed to all three of these substances, among 57 others, but from the SPC of the marketing authorization we were unable to establish the concentrations of sorbitol, ethanol or propylene glycol in the prescribed pharmaceuticals. We can only speculate that the maximum amount of the excipient would be equal to the difference between the mass of the pharmaceutical form minus the mass of the active substance in the preparation and then check the toxicity of the dose. The critically ill children who are receiving pharmaceutical preparations by continuous infusion are those who are most exposed to propylene glycol. Interestingly, our neonates were not exposed to benzyl alcohol, which has been recommended to be excluded from use in newborns due to its depressive effects on respiration and the central nervous system. As ethanol and propylene glycol are present in pharmaceutical preparations recommended for daily antirachitic prophylaxis (vitamin D preparations), every neonate in our study was exposed to the two most common excipients known to cause harm to this age group.

The types of excipients were first classified into 21 groups according to their function within the pharmaceutical preparation. It should be mentioned that a single substance used as excipient can have different functions in different drug formulations, for example, glycerol can be used as a cosolvent or as a sweetener in liquid formulations. Sorbitol can also be used as a stabilizer or as a sweetener in liquid formulations. Natural, semi-synthetic or synthetic sweeteners (acesulphame potassium, aspartame, glycerol, saccharin sodium, sorbitol and sucrose) are also frequently added to different pharmaceutical preparations and are of concern as they are cariogenic and affect glucose tolerance. Of these, acesulphame potassium and aspartame are known to be potentially harmful to neonates. In addition, aspartame as a source of phenylalanine is hazardous for newborns with phenylketonuria. In our study group, one antibiotic preparation for oral use contained both of these artificial sweeteners. Furthermore, saccharin sodium, present in three pharmaceutical preparations, is known to be harmful to neonates.

An important limitation of our study is in the definition of terms for the approved use of pharmaceutical preparations for a defined indication, a given age group, dosage and pharmaceutical form of administration, since many authors use different terms for the licensed and unlicensed use of medical products. According to a recent publication by Kimland and Odlind [25], we decided to use the terms ‘‘on-label’’ and ‘‘off-label’’, which sometimes makes comparisons among various studies and data difficult. There was a similar problem with the classification of excipients according to safety status, so we combined the data from Lass et al. and Turner et al. [6,10]. Like them, we also found that there was insufficient data on the quantities of excipients in given pharmaceutical preparations so we were unable to define the exact amount of excipients newborns were exposed to. Another limitation was our sample size, since we gathered information on drug use over a short period of time. Nevertheless, our findings add to the data on pharmaceutical preparations used in the newborn population and their consequent excipient exposure, as well as highlighting the need for monitoring safety concerns, analyzing the gathered clinical evidence and conducting further research studies in this field.

In conclusion, the results of our study show that newborns are receiving more pharmaceutical preparations for systemic then local treatment. They are mainly treated with off-label pharmaceuticals that are not approved for this population. We conclude that, while sick neonates are receiving effective medical products for their diseases or for prophylaxis, these preparations are not always safe for use in this age group, because they contain potentially and known to be harmful excipients. In the future, it will be necessary to test more pharmaceutical preparations and their excipients in this population and establish guidelines on how to adapt the results of clinical studies for pharmaceutical use in the neonatal period. It would be desirable that all the excipients and their quantities be labeled in the summary of product characteristics in the marketing authorization and those recognized as ‘‘known to be harmful’’ to newborns be omitted from these medical products.

**Declaration of interest**

The authors report no declarations of interest.

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