RESEARCH PAPER

Pharmaceutical Excipient Exposure in a Neonatal Intensive Care Unit

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Objective: To study the excipients exposure among neonates in a neonatal intensive care unit. **Method:** Prospective observational study was conducted from January, 2017 to June, 2019. Details of administered drugs were collected from the hospital case files. List of excipients of formulations and their quantities were collected from package insert leaflets or by contacting the manufacturers. Excipients were grouped into four categories based on available safety data. Calculated daily exposures to the excipients (mg/kg/day) were compared with adult acceptable daily intake. **Results:** More than half of the included 746 neonates were exposed to harmful excipients. 12.3% and 12.7% of neonates received higher than acceptable daily intake of sodium metabisulphite and sunset yellow FCF, respectively. **Conclusion:** There is a high risk of exposure of neonates to harmful excipients, and clinicians need to be aware of this during neonatal care.

Keywords: *Additives, Harm, Medications, Sodium metabisulphite*.

Excipients play a major role in converting medicinal agents to acceptable dosage forms [1]. Neonates are a vulnerable population and their drug handling, pharmacokinetic and pharmacodynamic aspects are different from older children. Neonates may be exposed to risks and unwanted effects of excipients when they are administered drug formulations. The reason could be immature physio-logical functions leading to inadequate metabolism and excretion of such excipients from body [2-4].

In the 1980s, ten neonatal gasping syndrome and death were reported in a study as a result of toxicity of benzyl alcohol (preservative) used in intravenous solutions [5]. Parabens, ethanol and propylene glycol are other examples of excipients having harmful effects in neonates [1]. Therefore, this study was conducted to assess types and amount of exposure to excipients among neonates in neonatal intensive care unit (NICU).

METHODS

This prospective observational study was conducted in the NICU of a tertiary care teaching hospital in Bangalore for duration of 2.5 years (January, 2017 to June, 2019) after approval from institutional human ethics committee. Valid consent was given by the parents/guardians of included study subjects who received at least one drug. Neonates dying within 24 hours of birth were excluded. Demographic details (gestational age, birthweight, gender, date of birth, post natal age), length of stay, daily clinical progress of neonates, information about prescribed medicines for all neonates (indication, dose, frequency, route of administration, dosage form and brand names) were recorded. Diagnoses were classified according to ICD-10 (International statistical classification of diseases and related health problems, 10th revision, 2016). Administered drugs were classified according to WHO Anatomical Therapeutic and Chemical (ATC) classification system.

Lists of excipients and their quantities present in each prescribed formulation were collected by referring to package insert leaflets (PIL) of drugs or contacting the manufacturers. Excipients were categorized into four groups as per Lass, *et al*. [1] *viz.,* (*a*) known to be harmful to neonates (adverse reactions reported in neonates); (*b*) potentially harmful (adverse reactions reported); (*c*) no safety data found (no data found in the literature on human exposure and toxicity); and (*d*) description of the excipient in PIL non-specific (description does not allow a specific literature search).

Statistical analyses: Daily exposure to excipients (mg/kg/day) were calculated based on available data on quantity of excipients in formulations, and were compared with acceptable daily intake (ADI) [6-8] for those which data of ADI was available.

RESULTS

Of the 790 cases admitted to NICU during the study period, 41 were excluded as they had received only phototherapy (no medications), and 3 babies died within 24 hours of birth. The baseline characteristics of 746 included neonates

are described in ***Table* I**. The most frequent diagnoses were respiratory distress of newborn, neonatal sepsis and congenital heart disease.

The total number of prescribed drugs was 5535, and 77 different drugs were given. Systemic anti-infectives, blood and blood forming organs, and alimentary tract and metabolism class were the most commonly prescribed classes of drugs. Intravenous (49, 63.6%) and oral (18, 23.3%) were the most common routes of administration.

The qualitative and quantitative information on excipients were available only for 35 and 15 drugs, respectively. Total of 27 different excipients were identified. Of all excipients, 4 (14.8%) and 10 (37%) were grouped under category a and category b, respectively. These excipients were present in 26% (20/77) of prescribed formulations, details of which, including safety concerns [1,6,9], are given in ***Table* III**. It was found that the highest proportion of above mentioned excipient were present in systemic anti-infectives.

Emulsifier 472 C was the only identified excipient of category c. Remaining excipients (8, 29.6%) including yellow and red oxides of iron, caramel colour and flavours were classified under category d. Daily exposure to excipients of 8 injections (vitamin K, adrenaline, amikacin, gentamicin, dexamethasone, heparin, midazolam and ranitidine), oxymetazoline hydrochloride nasal solution and paracetamol syrup were assessed and compared to ADI (***table* II**).

Table I Characteristics of Neonates (*N*=746)

Characteristics	*Value*
Male sex	424 (56.8)
Inborn babies	576 (77.2)
Gestational age, wk	
Term (≥37)	408 (54.7)
Moderate to late preterm (32 to <37)	274 (36.7)
Very preterm (28 to <32)	55 (7.4)
Extremely preterm (<28)	9 (1.2)
**Length of stay, d*	
Term	5.7 (0.91)
Moderate to late preterm	8.4 (0.80)
Very preterm	19.27 (4.90)
Extremely preterm	27.33 (4.16)
*Birthweight, g	2480 (700)

*All values in n (%) except *mean (SD).*

DISCUSSION

This study on qualitative and quantitative excipient exposure among hospitalized neonates in India found that 86.9% and 53.8% of neonates were exposed to at least one excipient known to be harmful or potentially harmful, respectively. Previous studies conducted in Brazil and Estonia found that almost all neonates were prescribed drugs containing at least one harmful excipient [1,3]. We found that harmful and potentially harmful excipients were present in formulations that were administered frequently and simultaneously. Hence neonates could be at greater risk of toxic effects. Similarly, Fister, *et al*. [10] reported that 51.6% of added excipients in formulations were potentially harmful and harmful ones.

Coloring agents (ponceau 4R, sunset yellow FCF, erythrosine and titanium dioxide) present in oral dosage forms were included in potentially harmful category. Regulatory status on colorants in different countries are not similar; in the European union, medicines containing sunset yellow and ponceau 4R must carry warning label concerning possible allergic reactions [6]. In our study, Ponceau 4R was most frequently observed colorant, though its use is banned in some countries due to its effect on neurocognitive development and behavior [2].

The use of category a or b excipients in intravenous/ oral formulations was much lesser in our study than findings of Lass, *et al*. [1]. However, in another study carried out in Spain [11], 32% of intravenous formulations

Table II Amount of Exposure to Excipients in Neonates (*N*=746)*

Excipient	*Adult ADI [6-8]*	*Daily dose exposure range*	*Comparison with adult ADI*
Sodium metabisulphite	0.7 mg/kg/d	0.09-2.1 mg/kg/d	‡Higher than ADI
Benzalkonium chloride	0.1 mg/kg/d	0.02-0.09 mg/kg/d	Within ADI range
Methyl paraben	10 mg/kg/d	0.03-1 mg/kg/d	Within ADI range
Propyl paraben	10 mg/kg/d	0.0003-0.09 mg/kg/d	Within ADI range
#Benzyl alcohol	5 mg/kg/d	0.016-1.3 mg/kg/d	Within ADI range
Phenol	<50 mg in 10 h period	0.1-0.8 mg in 12 h	Within ADI range
Sunset yellow FCF	2.5 mg/kg/d	0.3-4.2 mg/kg/d	^Higher than ADI

**Based on available data on quantity of excipients present in drugs; ADI: Acceptable daily intake; #should not be used in neonates; ‡12.3 % of exposures with use of adrenaline injection; ^12.7 % of exposures with use of paracetamol syrup.*

Table III Classification of Excipients to Which Neonates were Exposed*

Excipient category	*Functional category*	*Safety concern*	*Formulations containing excipients*
Known to be harmful to neonates			
Methyl paraben, *n*=713	Antimicrobial preservative	Hyperbilirubinemia in neonates, hypersensitivity reactions	Amikacin inj (*n*=405); Gentamicin inj (*n*=235); Dexamethasone inj (*n*=73)
Propyl paraben, *n*=713	Antimicrobial preservative	Hyperbilirubinemia in neonates, hypersensitivity reactions	Amikacin inj (*n*=405); Gentamicin inj (*n*=235); Dexamethasone inj (*n*=73)
Benzyl alcohol, *n*=108	Antimicrobial preservative, solvent	Fatal toxic syndrome in premature infants, metabolic acidosis, hypersensitivity, seizure, gasping	Heparin inj (*n*=93); Midazolam inj (*n*=15)
Benzalkonium chloride, *n*=5	Antimicrobial preservative, solvent	Skin irritation and hypersensitivity broncho-constriction in asthmatics	Oxymetazoline hydrochloride nasal solution
Potentially harmful			
Sodium metabisulphite, *n*=236	Antimicrobial preservative, antioxidant	Paradoxical bronchospasm, wheezing, chest tightness in asthmatic children	Adrenaline inj (*n*=74); Vitamin K inj (*n*=162)
Sodium carbonate, *n*=202	Alkalizing agent, buffering agent	Irritation to skin, eye, mucous membrane	Meropenem inj (*n*=202)
Sunset yellow FCF, *n*=74	Coloring agent	Anaphylactoid reactions, urticaria, angioedema	Paracetamol syp (*n*=71) Ibuprofen and paracetamol syp (*n*=3)
Ponceau 4R, *n*=114	Coloring agent	Anaphylactoid reactions, urticaria, angioedema	Domperidone susp
Phenol, *n*=188	Antimicrobial preservative, disinfectant	Hyperbilirubinemia, nephrotoxicity, anemia and may result in death	Ranitidine inj
Sodium bicarbonate, *n*=55	Alkalizing agent	Exacerbation of chronic heart failure in elderly, skin and eye irritant	Imipenem and cilastatin injection
Sodium deoxycholate, *n*=19	Detergent	Bradycardia, jaundice, lysis of red and white blood cells	Amphotericin B inj
Titanium dioxide, *n*=21	Coating agent, opacifier, pigment	Possibly carcinogenic	Sildenafil tablet (*n*=11); Paracetamol suppository (*n*=9); Clarithromycin granules for susp (*n*=1)
Erythrosine, *n*=67	Coloring agent	Concerns about carcinogenicity, toxic to human lymphocytes *in vitro*	Vitamin D and calcium syp (*n*=67)
Calcium chloride, *n*=44	Antimicrobial preservative, water absorbing agent	Stomach and heart disturbance, dermatitis	Lung surfactant

**According to available safety data [1,6,9]; Inj-injection; Susp-suspension; Syp-syrup.*

and 62% of oral formulations contained at least one harmful excipient. These differences can be explained by the availability of information of excipients present in formulations in different countries. We found high rates of exposure (higher than ADI) to sodium metabisulphite and sunset yellow FCF. Similar findings were reported by Akinmboni, *et al*. [12] that 11% of neonates were exposed to a higher amount of an excipient than the FDA/WHO recommended adult dose.

Daily exposure to phenol (in ranitidine injection) was within the adult ADI range. However, literatures show that use of ranitidine in very low birth weight neonates can increase incidence of necrotizing enterocolitis, mortality and infection [13]. Safety concern regarding use of ranitidine was reported to the neonatologist. Daily exposure to benzyl alcohol did not exceed the adult ADI. However, as per FDA recommendation and label of the heparin injection, benzyl alcohol containing formulations

WHAT THIS STUDY ADDS?

- It is advisable that excipient exposure be assessed while selecting medicinal formulations for neonates.

should not be used for neonates and premature infants due to risk of fatal toxic syndrome in neonates [6,14-16]. Unfortunately, 14.5% of neonates were exposed to benzyl alcohol containing formulations. For 12.5% of exposures, alternative preservative free formulation with the same concentration of heparin sodium injection and similar cost was available, which were suggested to the neonatologist. Another study conducted in Netherlands showed that oral liquid medicines without potentially harmful excipient were available for 22% of medicines [17].

An important limitation of the present study was the lack of data on neonatal ADI of excipients due to barriers to conduct such studies. Another limitation was lack of information about list of excipients and their quantities present in each formulation. So, we could not assess the extent of exposure to all excipients of formulations. However, our findings with limited available data show that exposure to harmful excipients is high, and awareness regarding their risks needs to be raised.

Substitution of those medications with excipient (harmful) free formulations, at least in high risk conditions, will avoid unwanted risks. It is also important that manufacturers disclose detailed qualitative and quantitative information of excipients of formulations to clinicians and clinical pharmacists, for risk/benefit assessment of selection of drugs for neonates.

Ethical clearance: VIPS Human Ethics Committee; IEC/2016-14 dated December 09, 2016.
Contributors: SN: collected the data, analyzed the data and wrote the manuscript; NKM: designed, monitored and supervised the study and approved the final manuscript; SB: was the neonatologist who co-supervised the study.
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REFERENCES

1. Lass J, Naelapää K, Shah U, Käär R, Varendi H, Turner MA, *et al*. Hospitalized neonates in Estonia commonly receive potentially harmful excipients. BMC Pediatr:2012; 12:136.
2. 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: F236-40.
3. Souza A Jr, Santos D, Fonseca S, Medeiros M, Batista L, Turner M, *et al*. Toxic excipients in medications for neonates in Brazil. Eur J Pediatr: 2014;173:935-45.
4. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-Drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157-67.
5. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med.1982;307:1384-8.
6. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients, 6th ed. Pharmaceutical press; 2009.
7. Commission of the European Communities. Report from the Commission on Dietary Food Additive Intake in the European Union. Available from: *https://ec.europa.eu/transparency/regdoc/rep/1/2001/EN/1-2001-542-EN-F1-1.Pdf.*Accessed January 10, 2019.
8. European food safety authority (EFSA). Reasoned opinion on the dietary risk assessment for proposed temporary maximum residue levels (MRLs) of didecyldimethy-lammonium chloride (DDAC) and benzalkonium chloride (BAC). Available from: *https://efsa.onlinelibrary. wiley. com/doi/epdf/10.2903/j.efsa.2014.3675*. Accessed January 13,2019.
9. European Medicines Agency.Committee for Medicinal Products for Human Use (CHMP). Reflection Paper: formulations of choice for the paediatric population. Available from: *https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf*. Accessed December 12, 2018.
10. Fister P, Urh 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;28:2053-61.
11. Garcia-Palop B, Movilla Polanco E, Cañete Ramirez C, Cabañas Poy MJ. Harmful excipients in medicines for neonates in Spain.Int J Clin Pharm. 2016;38:238-42.
12. Akinmboni TO, Davis NL, Falck AJ, Bearer CF, Mooney SM. Excipient exposure in very low birth weight preterm neonates. J Perinatol. 2018;38:169-74.
13. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, *et al*. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics: 2012;129:e40-5.
14. Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. Pediatrics:1983;72:356-8.
15. Hiller JL, Benda GI, Rahatzad M, Allen JR, Culver DH, Carlson CV, *et al*. Benzyl alcohol toxicity: Impact on mortality and intraventricular hemorrhage among very low birth weight infants. Pediatrics: 1986;77:500-6.
16. CDC. Neonatal deaths associated with use of benzyl alcohol-United States. Available from: *https://www.cdc.gov/mmwr/preview/mmwrhtml/00001109.htm*. Accessed August 13, 2018.
17. Van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM. The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol:2011;72:465-73.