EVALUATION OF EXCIPIENTS USED IN PAEDIATRIC COMPOUNDED FORMULATIONS PRESCRIBED IN A NEONATAL INTENSIVE CARE UNIT

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BACKGROUND AND IMPORTANCE

The absence of marketed medicines adjusted to the pathophysiological profile of the neonate often implies the preparation of personalized compounded medicines. To meet therapeutic needs and improve medicines' stability, several vehicles have been developed and studied for different drugs. The choice of excipients is a critical point in paediatric compounded formulations (PCF), as there are limits inherent to the target population.

AIM AND OBJECTIVES

Evaluation of exposure to PCF excipients, according to individualized medical prescriptions to patients admitted to a Neonatal Intensive Care Unit (NICU), between 9/2019 and 8/2020, considering the recommended limits. Search for related adverse events (AEs) when limits are exceeded. Propose solutions for the non-conformities detected.

MATERIALS AND METHODS

1. Definition of excipients to be evaluated, search of the respective recommended limits and AEs reported in the bibliography (Table I).
2. Ranking PCF containing at least one of the selected excipients and calculation of its concentration in the formulation.
3. Analysis of prescriptions, calculation of excipient/patient daily intake and evaluation according to age recommendations.
4. In cases where the limits were exceeded, search the patient's medical record for AEs that may be related to exposure to the excipient.

RESULTS

Considering the 10 selected PCF, present in 86 prescriptions corresponding to 172 exposures, only 2 of the evaluated excipients were found: Propylparaben and Propylene glycol (PG) (Table II). In 52 exposures there was ingestion above recommended limits, 50 of which were of PG in neonates with less than 28 days of age (Table III, IV). Five records of AE described in bibliography with a causal link were found in the medical files (Table V).

Table I - Problematic excipients evaluated

Excipients	Maximum recommended daily dose	Adverse Reactions/Considerations
Benzyl alcohol	Contraindicated in neonates 5mg/kg/day (>4 weeks) [3,6]	Metabolic acidosis, respiratory depression and neurotoxicity[2,9]
Benzoic acid/ Sodium benzoate	5mg/kg (total)[4]	Increases free bilirubin and risk of kernícterus Not recommended in neonates[2]
Ethanol	6mg/kg (<6 years)[8]	Respiratory depression, neurotoxicity and cardiovascular toxicity[6,8] Avoid in pediatric formulations
Propylene glycol	1mg/kg (up to 28 days) 50mg/kg (> 29 days to 4 years)[2]	Cytotoxicity; Seizures; cardiovascular effects; Neurotoxicity; Respiratory depression, lactic acidosis, oral laxative effect due to hyperosmolarity[10]
Propylparaben	2mg/kg[5]	Avoid in neonates; Hyperbilirubinemia in neonates; hypersensitivity reactions Cumulative toxic effect[5,6]
Polysorbate 80	10mg/kg[7]	E-ferol sindrome in preterm neonates (thrombocytopenia, renal dysfunction, hepatomegaly, cholestase, ascites, hypotension, metabolic acidosis)[7]
Sorbitol	5mg/kg (≤2 years) 140mg/kg (> 2years)[2]	Contraindicated in patients with hereditary fructose intolerance (metabolized to fructose) Osmotic diarrhea, flatulence; abdominal distention; malabsorption syndrome; liver damage; coma[1,2]

Table II – Quantitative composition in problematic excipient (mg/mL) per formulation

Paediatric Compounded Formulation	Propylparaben (mg/mL)	Propylene glycol (mg/mL)
Acetylsalicylic Acid 20 mg/mL	0.30	9.44
Ursodeoxycholic Acid 12,5 mg/mL	0.79	24.73
Biotin 2,5 mg/mL	0.30	9.44
Spironolactone 2,5 mg/ mL	0.30	9.44
Phenobarbital 10 mg/ mL	0.30	9.44
Flecainide 5 mg/mL	0.35	11.13
Chloral Hydrate 100 mg/mL	0.55	17.31
Propranolol 1 mg/mL	0.79	24.73
Ranitidine 25 mg/mL	0.79	24.73
Trimethoprim 10 mg/mL	0.30	9.44

Table III - Daily dose of ingested propylene glycol (mg/kg/day)

Paediatric Compounded Formulation	Posnatal age							
	≤28 days				>28 days			
	N total	N (>1mg/kg/d)	Min	Max	N total	N (>50mg/kg/d)	Min	Max
Trimethoprim 10 mg/mL	12	11	0.96	1.93	2	0	1.89	1.93
Acetylsalicylic Acid 20 mg/mL	0	0	.	.	2	0	2.29	2.36
Ursodeoxycholic Acid 12,5 mg/mL	0	0	.	.	2	0	39.57	43.97
Spironolactone 2,5 mg/ mL	2	2	7.43	7.73	8	0	3.65	14.91
Phenobarbital 10 mg/ mL	2	2	5.58	6.94	8	0	0.49	9.78
Chloral Hydrate 100 mg/mL	24	24	5.32	17.13	11	0	6.69	26.54
Propranolol 1 mg/mL	5	5	40.77	76.30	1	0	30.50	30.50
Ranitidine 25 mg/mL	3	3	1.00	6.03	1	0	4.45	4.45
Flecainide 5 mg/mL	1	1	9.16	9.16	0	0	.	.
Biotin 2,5 mg/mL	2	2	12.89	17.32	0	0	.	.

N total: number of prescriptions per preparation;
N>mg/kg/d: number of prescriptions in which the daily dose exceeds the recommended dose for age

Table IV - Daily dose of ingested propylparaben (mg/kg/day)

Paediatric Compounded Formulation	Propylparaben (mg/kg/d)			
	N total	N (>2mg/kg/d)	Min	Max
Trimethoprim 10 mg/mL	14	0	0.03	0.06
Acetylsalicylic Acid 20 mg/mL	2	0	0.07	0.075
Ursodeoxycholic Acid 12,5 mg/mL	2	0	1.26	1.40
Spironolactone 2,5 mg/ mL	10	0	0.11	0.47
Phenobarbital 10 mg/ mL	10	0	0.015	0.31
Chloral Hydrate 100 mg/mL	35	0	0.00	0.84
Propranolol 1 mg/mL	6	2	0.97	2.42
Ranitidine 25 mg/mL	4	0	0.03	0.19
Flecainide 5 mg/mL	1	0	0.29	0.29
Biotin 2,5 mg/mL	2	0	0.41	0.55

N total: number of prescriptions per preparation;
N>2mg/kg/d: number of prescriptions in which the daily dose exceeds the recommended dose

Table V - Adverse reactions with possible causal link

Paediatric Compounded Formulation	Registration in medical files of described adverse reaction	Suspected excipient
Propranolol 1 mg/mL	Hyperbilirubinemia	Propylparaben
	Cardiovascular ADRs (bradycardia); Respiratory depression	Propylene glycol
	Hyperbilirubinemia	Propylparaben
	Cardiovascular ADRs (bradycardia);	Propylene glycol
	Diarrhoea that normalized after drug suspension	Propylene glycol

CONCLUSIONS AND RELEVANCE

In cases of formulations where exposure to excipients exceeded the recommended limits, an alternative with a different composition or concentration should be investigated. As 50 out of 52 non-compliances were with PG, used as a solvent in the paraben concentrate, this formulation will be tested using water instead of PG. It was not possible to retrospectively confirm a causal assessment related to the AE found as these are common clinical conditions in these patients. Individualization of medication through compounding is the right direction as it best suits the patient's profile. However, the choice of excipients is crucial for patient safety.

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