IMPLEMENTATION OF A STRATEGY TO OVERCOME THE POTENTIAL TOXIC EFFECTS OF PROPYLENE GLYCOL IN NEONATES

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BACKGROUND AND IMPORTANCE

The available evidence on the safety of excipients in compounded formulations is somewhat limited. Contributing to a higher level of evidence seems relevant, particularly for the design and preparation of compounded formulations for use in neonatology.

We have previously carried out a study on the presence of problematic excipients in oral compounded formulations for neonates (1), in which we reported intake above the recommended limits, mainly of propylene glycol (PG), in neonates under 28 days of age.

AIM AND OBJECTIVES

To implement a strategy aimed at overcoming the potential toxic effects due to the exposure of neonates to the excipient PG, commonly present in oral compounded formulations for use in neonatology.

MATERIALS AND METHODS

Evaluation of the composition of compounded formulations regularly used in a Neonatal Intensive Care Unit to identify the source of PG.

Assessment of alternatives, considering their preservative power, by calculating the concentration of parabens, and analysing the solubility of the chemical forms of parabens used.

RESULTS

- ✓ The source of the PG in the formulations was the preservative solution used – Parabens Concentrate (B.8), from the Portuguese Galenic Formulary (FGP) (2).
- ✓ As an alternative to B.8, we evaluated 3 paraben solutions described in the literature, taking into account the respective parabens concentrations, the nature of the solvent and the reported stability. Since the parabens concentrations were at least 100-fold lower than that of the B.8, we decided not to adopt any of the solutions described, once this could compromise the preservation of the formulations (TABLE I).

TABLE I - PARABENS SOLUTIONS EVALUATED

SOLUTION	Methylparaben	Propylparaben	Propylen glycol	Water	Expiry	Storage conditions	Parabens concentration (m/V)
Parabens Concentrate (FGP B. 8) (2)	70g	30g	944g		365 days	Room Temperature. Light Protection.	10% parabens
Aqua conservans (3)	0.5g	0.22g		*qs* 1000mL	180 days	Room Temperature. Light Protection.	0.072% parabens
Preservative water without propylene glycol (4)	0.8g	0.2g		*qs* 1000mL	180 days	Room Temperature. Light Protection.	0.1% parabens
Hydroxybenzoates preservative solution (5)	0.8g	0.2g	9g	*qs* 1000mL	180 days	Room Temperature. Light Protection.	0.1% parabens
Parabens Aqueous Concentrate (prepared with parabens sodium salts)	70g (sodium methylparaben: 80g)	30g (sodium propylparaben:34g)		*qs* 1000mL	180 days	Room Temperature. Light Protection.	10% parabens

- ✓ In an alternative approach, the preparation of a 10% parabens concentrate in water, instead of PG, was implemented. To promote the dissolution of methylparaben and propylparaben (7:3) in water, the respective sodium salts were used (TABLE II). The solution was prepared after calculating the respective equivalent concentrations.

TABLE II - PARABENS SODIUM SALTS EQUIVALENTS

	M (g/mol)	Concentration (g/mL of FGP B8 Parabens Concentrate)	Equivalent concentration of sodium salt (g/mL)	Water solubility (6)
Methylparaben	152.1	0.07	…..	1 part in 400 parts of water; 1 in 50 of water 80ºC
Sodium Methylparaben	174.1	…..	0.08	Freely soluble in water
Propylparaben	180.2	0.03	…..	1 part in 2500 parts of water; 1 in 400 of boiling water
Sodium Propylparaben	202.2	…..	0.034	Freely soluble in water

CONCLUSIONS AND RELEVANCE

A water-based, PG-free paraben preservative solution has been developed, suitable for preserving oral compounded formulations. This strategy makes it possible to overcome the potential toxic effects of PG in neonates, thereby increasing the safety of the formulations.

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