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Short communication

Excipients in pediatric dosage forms and related regulatory aspects with review to propylene glycol

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Introduction

Pediatric formulations often contain excipients with lack of safety and toxicity data based on a unique and daily exposure, duration of treatment and patient acceptability. In the 1980s, US set up regulatory initiatives for the development of pediatric drugs. In 2007, pediatric regulation focused on the development of high-quality pediatric formulations for children 0-17 years old entered into force in the EU. The European Medicine Agency (EMA) activities on medicines for children is coordinated by the Pediatric Committee (PDCO), with roles to: (i) ensure full compliance with pediatric regulation, evaluate and adopt opinions on pediatric investigation plans (PIP) for development of pediatric medicines submitted by pharmaceutical companies and include studies evaluating safety and quality to support the authorization, (ii) verify that all measures agreed in PIP have been conducted, (iii) issue waivers supported with evidence that the medicine is unsafe or without significant benefits compared to existing treatments and (iv) contribute to the development of network of centers with expertise for clinical studies in children (Dunne, 2007).

The US and European Pediatric Formulation Initiatives (USPFI and EUPFI) are coopreating with Food and Drug Administration (FDA) and EMA as observers in order to address safety problems linked to excipients used in children, create platforms for systematic evaluation of excipient's safety in children and newborns, generate evidence-based database (safety and toxicity aspects of pharmaceutical excipients - STEP) to facilitate access to the data, provide rapid evaluation of the risks due to the use of excipients and improve the decision making during pediatric medicines design.

The aim of the present work was to address the safety and toxicity aspects of the excipient propylene glycol (PG) and the risk associated with its use in pediatric medicines.

Methods

Literature search was performed using relevant databases: PubMed, Scopus, Medline, by keywords: propylene glycol, PG, PG toxicity, pediatrics, neonates, published between 2010-2022, including case reports, retrospective and prospective studies, prospective controlled observational studies, and review articles.

Results and discussion

The cases are reporting data on children of a broad age spectrum, being administered high PG dose levels by various administration routes. PG (1,2-propanediol) is an organic compound used as drug solvent, moisturizer, cosolvent, solubilizer in medicines. Although generally considered as safe for use as a vehicle in medicines, PG toxicity has been reported during treatment of newborns and children with age-inappropriate dosage forms. EMA guidelines adhere to a safety threshold of 50 mg-kg/day in children below 5 years and 1 mg-kg/day in neonates based on the low clearance of PG in this age group. The pharmacokinetics of PG in children is unknown nor the long-term effects of PG accumulation. Short-term harms and serious adverse effects of PG especially in newborns are often described following topical, oral and IV administration. PG is eliminated through the kidneys or metabolized in the liver through alcohol dehydrogenase (ADH) to lactate and pyruvate and both elimination routes are dose and concentration dependent. PG clearance is low in neonates showing long plasma life, with a half-life

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10.8-30.5h compared to 5h in adults. Therefore, neonates are at high risk of PG accumulation and adverse effects due to toxicity. Children under 4 years old are also prone to PG accumulation due to the limited metabolic capacity (ADH). Laboratory values that can assist in making the decision for PG intoxication are serum PG concentrations, osmolality, lactate and pyruvate concentrations, bicarbonate levels, serum creatinine, and anion gap. Hyperosmolarity and metabolic acidosis lead to hemolysis, renal failure, CNS depression, seizures, and cardiovascular decompensation. If the diagnosis is not established clinical deterioration may progress to multisystem organ dysfunction, sepsis and systemic inflammatory response syndrome (Glasgow et al., 1983). PG toxicity is reported when anti-epileptics, sedatives, topical silver sulfadiazine, and multivitamins (parenteral nutrition) are used at hospital units. However, due to the shortage of age- appropriate medicines in clinical practice, pediatric patients are often exposed to potentially harmful excipients above age-recommended values.

MR Spectroscopy results from retrospective cohort study including 45 neonates born at 24–42 weeks gestational age (January 2016-2019), treated with IV phenobarbital, pointed to long PG half-life in neonatal brain, leading to short and long-term adverse effects. PG renal and enzyme (ADH) clearance pathway depend on the birth weight and postnatal age, mainly due to elimination processes and metabolic pathways immaturity during the first month of life (Van de Lagemaat et al., 2021). Combination of PG with ethanol or other excipients metabolized/excreted by the same pathways will compromise the elimination in neonates and premature neonates leading to cardiac, renal or respiratory problems. Serious health problems due to PG and ethanol toxicity are documented when Kaletra® (lopinavir/ritonavir) for oral use dissolved in ethanol (356.3 mg ethanol mL^{-1}) and PG (152.7 mg mL^{-1}) was used in premature neonates (FDA Drug safety communication., 2011).

Acute renal failure secondary to PG overdose with single high-dose vit. D (Stosstherapy) was reported in 7 months-old infant treated with 600,000 units of ergocalciferol (solution containing 77.7 g of PG). According to the WHO, this exceeds the maximum tolerable amount of 25 mg-kg/day, and may cause acute renal failure, metabolic acidosis and hyperkalemia (Jelley et al., 2019).

Oral citrate supplementation in 6-week-old neonate diagnosed with renal tubular acidosis led to PG neurotoxicity. The therapy composed of sodium citrate solution and the potassium citrate/citric acid solution, both containing 2% v/v PG, was administered for 6 days before the onset of the symptoms. The PG intake was 222 mg-kg/day and the PG plasma levels were highly elevated. Besides the pharmacokinetics and long half-life of PG in infants, the infant was exposed to larger risk of PG toxicity due to higher doses of citrate supplementation (Khan et al., 2020). Although the emphasis has been given to PG in liquid preparations, before administration of age-inappropriate liquid dosage forms in pediatric patients, additional potentially harmful excipients levels and their daily administered amount have to be identified and compared to the cut-off values for safe exposure by age.

Conclusion

Numerous case reports and available PG pharmacokinetic models in neonates and children made the health professionals aware of large variability as well as weight and age dependent PG exposure accompanied with dose dependent kinetics. Permitted EMA daily exposure to PG limits from medicines used in pediatric patients (neonates, 1 month to 4 years, 5 years up to 17 years and adults) for different types of administration (except for inhaled PG), are conservative but should be used with caution in children less than 4 years old due to insufficient data for safety in this population, especially in patients with impaired renal or metabolic clearances or receiving multiple medicines which increases the risk of metabolic interaction and exposure to different excipients with similar clearance/metabolic pathways.

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