SAFETY AND TOXICITY OF PHARMACEUTICAL EXCIPIENTS IN THE PEDIATRIC POPULATION

Cabral, P.R.[1*]; Nicoletti, C.D.[1]; Futuro, D.O.[1]
[1] *Universidade Federal Fluminense, R. Dr. Mário Vianna, 523 – Santa Rosa, Niterói, Rio de Janeiro, Brasil.*
priscilarc@id.uff.br

Introduction

Pediatric pharmaceutical care has several challenges, such as ensuring access to safe and effective medicines and the availability of appropriate pharmaceutical formulations for children (JOSEPH; CRAIG; CALDWELL, 2015; CASTRO et al., 2018). The excipients are used in pharmaceutical preparations to support maintenance parameters as compatibility, stability (chemical, physical and microbiological), dissolution, bioavailability, and palatability of the drug. However, in recent years, excipient toxicity in pediatric patients has gained prominence in the scientific literature as case reports of toxicity in children (SALUNKE; GIACOIA; TULEU, 2012; KOGERMANN et al., 2017). In this context, the use of excipients in pediatric medicines must consider their potential to induce adverse reactions in children, given their organs' immaturity and inherent physiological processes (FABIANO; MAMELI; ZUCCOTTI, 2011). This study aims to review the scientific evidence regarding the safety and toxicity of pharmaceutical excipients in children.

Material and Methods

This study is a literature review carried out from April to June 2021 to identify excipients with the potential to harm children. The search was performed in the Scopus and PubMed databases, using the descriptors “pediatrics”, “excipients” and “safety”. Studies addressing potentially harmful excipients to the pediatric population, published in Portuguese and/or English from January 2012 to June 2021, were selected. Duplicate publications in the databases were excluded. The data gathered was analyzed using descriptive statistics.

Results and Discussion

The research in the databases resulted in 123 publications. After reading the titles and abstracts, 30 publications were selected for a full-text reading, followed by a final list of 16 relevant publications. The main excipients potentially harmful to the pediatric population identified in this review play the role of preservatives, diluents and surfactants. Most of the restrictions on the excipients use were due to adverse reactions targeted at neonates and children under three years of age. In this sense, the child's age group played a decisive role in the development of adverse reactions. Parabens (n: 16), propylparaben (n: 6), methylparaben (n: 4) and ethylparaben (n: 1); benzoates (n: 22), benzyl alcohol (n: 9), sodium benzoate (n: 6), benzoic acid (n: 4); ethanol (n: 12) l; propylene glycol (n: 11) and polysorbates (n: 10) have shown potential for the occurrence of adverse reactions in children. The most cited excipients with the potential to cause adverse reactions in the pediatric population refer to parabens (n: 27), including the terms "parabens", "propylparaben", "methylparaben" and “ethylparaben”. Hypersensitivity reactions were more associated with parenteral use of parabens in neonates. In addition, caution should be exercised in the exposure of children allergic to acetylsalicylic acid and jaundiced newborns. The studies have shown that benzoates, distributed in "benzyl alcohol", "sodium benzoate", “benzoic acid" and "benzoates" are associated with greater impairment in children under three years of age. Benzoates, commonly used as preservative agents,

have been described primarily as responsible for hypersensitivity reactions. The use of benzyl alcohol in children was associated with respiratory, cardiovascular and neurological impairment. Also, the risk of hyperbilirubinemia and metabolic acidosis was observed. As for benzoic acid, there was a predominance of reports of bronchoconstriction in asthmatic patients. Although ethanol and propylene glycol are prominent in the development of drugs as solvents, exposure to these excipients is often associated with adverse reactions in the pediatric population. Studies have found that ethanol can cause cardiovascular, respiratory, gastrointestinal, neurological, and metabolic toxicity, with restricted use in children under 12 years of age. Propylene glycol, on the other hand, should be avoided in children under four years of age due to its known ability to cause damage in children, given the immaturity of the organs responsible for its metabolism. Potential adverse reactions described include nephrotoxicity, hypotension, biochemical and neurological toxicities. Polysorbates, referred to as "Polysorbate 80" (n: 7) and "Polysorbates" (n: 3), has been shown to be responsible for the E-Ferol Syndrome in neonates, characterized by thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis. Studies have also pointed to potential effects on the blood-brain barrier and drug interactions due to inhibition of p-glycoprotein. It should be noted that these effects are related to the dosage to which the patient was exposed. Studies have proposed that the development of a model for the determination of the specific daily intake for children and neonates can help in the safe use of these excipients.

Conclusion

Adverse cardiovascular, respiratory, gastrointestinal, neurological, metabolic and hypersensitivity reactions associated with the use of excipients in children have been observed. The selection of excipients for medicines intended for the pediatric population must, therefore, consider the occurrence of adverse reactions in this population as a way to make safer medicines viable for children.

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