A REVIEW OF THE EXPOSURE TO POTENTIALLY HARMFUL EXCIPIENTS THROUGH ORAL LIQUID FORMS IN PEDIATRIC INPATIENTS IN FRANCE

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Background and importance

The pediatric population experiences an important heterogeneity in pharmacokinetics and pharmacodynamics parameters during its development, resulting in differences in drug efficacy and toxicity particularly for neonates. These differences have been studied for active molecules; but the impact on the pharmacological parameters of excipients remains less well known. Nowadays, various initiatives have been started to gather information on the specific toxicity of excipients such as the KIDS list or the STEP database.

Aim and objectives

This study consisted in a survey of the qualitative and quantitative composition of a large panel of pediatric oral liquid medicines in order to identify the most common excipients found in these formulations.

Considering toxicity data and daily recommended limit available for these excipients, the objective was then to verify whether the excipient composition of pediatric oral liquid forms are adapted for this population.

Material and methods

A compilation of the composition in excipients of oral liquid forms prescribed in French pediatrics and neonatology departments was established from the summary of product characteristics (SPC). Then, for excipients found in more than 10% of the drugs listed, a review of their toxicity data was carried out using the STEP Database. Finally, in a selection of 10 largely used drugs, the daily-administered amounts of excipients have been calculated based on the recommended posology in SPC and compared to the recommended daily limits proposed by the European Medicine Agency (EMA).

Results

219 formulations were studied

123 active substances

140 excipients

16 excipients found in ≥ 10% of the formulations

10 were known as excipients of interest (EOI)

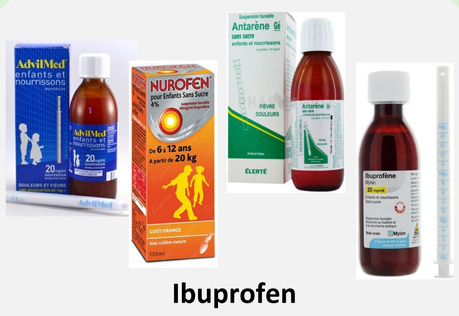
Most represented EOI in the studiedoral liquid forms and their recommended maximum daily intake

Excipients (% of formulations)	Function	Main toxicity	Recommended maximum doses (EMA)
Methylparaben (31%)	Preservative	Anaphylaxis, hormone levels perturbation	10mg/kg/day sum of methyl + propyl + ethyl paraben
Saccharose (27%)	Sweetening agent	Dental, obesity	5mg/kg/day for patients with HFI, 5g per day for diabetic patients
Sodium benzoate (26%)	Preservative	Jaundice, metabolic acidosis	5 mg/kg/day (contraindicated in newborns)
Propylparaben (25%)	Preservative	Anaphylaxis, hormone levels perturbation	2mg/kg/day (10mg/kg/day for the sum of methyl + propyl + ethyl paraben)
Xanthan gum (21%)	Viscosity increasing / emulsifying / suspending agent	Gastrointestinal	No recommendation
Glycerol (18%)	Solvent/humectant	Gastrointestinal	10g per dose
Propylene glycol (16%)	Solvent/humectant	Neurological, cardiac, gastrointestinal	Neonates : 1 mg/kg/day < 4 years : 50 mg/kg/day ; ≥5 years : 500 mg/kg/day
Sorbitol (14%)	Sweetening agent/viscosing agent	Gastrointestinal, contraindicated if hereditary fructose intolerance (HFI)	140 mg/kg/day, 5mg/kg/day for patients with HFI
Ethanol (13%)	Solvent/preservative	Neurological	<2years old : avoid; 2-5yo : 6 mg/kg ; >6y : 75mg/kg/day
Aspartame (13%)	Sweetening agent	Metabolic, contraindicated if phenylketonuria	40 mg/kg/day per day , avoid < 12 weeks old

Analyzed formulations :

Paracetamol oral suspension

Paracetamol sachets



Ibuprofen

Furosemide LASILIX®

Captopril NOYADA®

10 active substances

32 formulations

ARROW
ALMUS
BIOGARAN
CRISTERS
EG
VIATRIS
RANBAXY
SANDOZ
TEVA
ZYDUS
ZENTIVA

Amoxicillin/Clavulanic acid AUGMENTIN® and generic brands

Azithromycine ZITHROMAX®

Amphotericin B FUNGIZONE®

ARROW
BIOGARAN
EG
ZENTIVA

Betamethasone CELESTENE® and generic brands

Ergocalciferol STEROGYL®

6 (19%) out of the 32 formulations respect age limit and acceptable daily intake

This represents **3 molecules** on the 10 studied

Conclusion - Perspectives

Hospitalized children and neonates are receiving a wide range of excipients that have shown toxicities. Although studies tend to enlarge the knowledge about their specific use and toxicity in pediatrics, too little remains known about their impact in these populations, especially in preterm. This study showed that recommended daily intakes are not reached with current posologies, particularly with association of several drugs, which can lead to addition of excipients and therefore addition or combination of toxicities. When EOI cannot be avoided, as alternatives cannot always be found, quantitative information about their amount in drug formulations should be easily known to help pharmacists and physicians to select the most appropriate drugs and anticipate possible adverse effects or even adapt drugs posology. An alternative is the production of magistral preparation for these population, with less possible use of EOI. In parallel, new galenic approaches allow to complete the therapeutic arsenal in pediatrics such as mini-tablets or 3D-printing, which tends to enrich a personalized medicine.

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toxicity