

Safe excipient exposure in neonates and small children – protocol for the SEEN project

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ABSTRACT

INTRODUCTION: The pharmacokinetics of excipients in neonates differs from that of older children. In a recent pan-European survey, two thirds of neonates received at least one potentially harmful excipient, such as ethanol and benzoates. The content of sweeteners varied by route of administration (more common by enteral than parenteral route) and regional differences were revealed. The survey did not identify if the content of excipients was more pronounced in medications prescribed for specific medical diseases, e.g. more common in cardiovascular conditions than lung diseases. Furthermore, the quantitative amount of e.g. ethanol in the multi-medicated neonate has not been investigated. The aim of the present study is to quantify the total amount of excipients administered to poly-medicated neonatal and paediatric patients during hospitalisation; and to investigate if any particular medical diseases are treated with potentially harmful excipients.

METHODS: This is a retrospective cohort study based on chart-audit on multi-medicated patients ≤ 5 years of age treated at the Rigshospitalet, Denmark. Preparations with ethanol, propylene glycol, benzyl alcohol, parabens, acesulfame p, aspartame, glycerol, sorbitol and polysorbate-80 will be recorded and cumulative amounts will be calculated.

CONCLUSION: By quantifying the amount of harmful excipients to which paediatric patients are exposed, the study will contribute to a risk/benefit assessment of the medication standards of neonatal and paediatric patients.

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TRIAL REGISTRATION: This study was registered at clinicaltrials.gov (reg. no. NCT02545712).

Development of paediatric formulations, particularly those suitable for neonates and young children, can be challenging. There is only limited knowledge available on the acceptability of different dosage forms, tastes, and – importantly – the safety of formulation excipients in relation to children's age and development stage. In general, pharmaceutical excipients exhibit many critical functions that are necessary to maintain, e.g. the quality and palatability of the active pharmaceutical ingredient (API) drug, without being pharmacologically active themselves [1].

Despite their widespread use in both licenced and unlicensed medications [2, 3], our knowledge about the

safety characteristics of these "inert" excipients remains very limited [4]. Some can be classified as "acceptable" or "neutral" because their use triggers no safety concerns, whereas others may be considered "controversial" as their use can be associated with certain risks of adverse drug events. Excipients such as benzyl alcohol and polysorbate-80 have previously been associated with increased mortality in neonates [5, 6] and methyl-paraben and propyl-paraben have been linked with cases of hyperbilirubinemia [7] in the same population, whereas artificial sweeteners such as aspartame and acesulfame potassium (previously acesulfame p) may decrease insulin sensitivity in neonates [8]. The preservatives ethanol and propylene glycol serve as solvents and microbial preservatives and are some of the most commonly used solvents in oral liquid medications [9]. Both are known to affect the development of the central nervous system (CNS) [3, 10, 11] and may thus be characterised as harmful. Studies and observations on foetal alcohol effects in children give direct evidence of the grave deleterious effects of chronic ethanol exposure, for example, on neurological and cognitive developmental processes [12].

Ethanol intake secondary to medication administration was recently measured in 15 neonates [13]. The study measured the blood ethanol levels after administration of one or a maximum of two ethanol-containing preparations. Approximately one third of blood ethanol levels were above the recommendations of the European Medicines Agency following a single dose of one or two ethanol-containing medications. Especially in preterm and term neonates, the immature metabolic pathways will affect the clearance of both the active pharmaceutical ingredient and the excipients. Further, some excipients and APIs are metabolised by some of the same enzymatic pathways [14], e.g. ethanol and paracetamol. Thus, the vulnerable multi-medicated neonatal and young paediatric patient may be at increased risk of accumulating toxic levels of the API and/or the excipient of interest (EOI) [14]. Despite their "non-pharmacological" activity, excipients may pose a health risk to both the short-term and the long-term well-being of the patient if the exposure exceeds clinically relevant levels [9]. The harmful effects include ethanol-induced CNS depression [3] and foetal alcohol syndrome [12]. Furthermore, propylene glycol

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has been associated with ethanol-like-intoxication and neurotoxicity [15], whereas both benzyl alcohol and polysorbate-80 in medication have resulted in death among low-birth-weight infants [5, 6]. Though several studies have described the potentially harmful effects of ethanol in neonates and young children, a narrative study from 2014 was unable to describe an international consensus on ethanol-tolerance levels in neonates or young children [15]. Moreover, the American Association of Paediatrics (AAP), the Food and Drug Administration (FDA) and the European Medical Agency (EMA) currently propose different limits for the level of tolerable ethanol in medication to neonates and young children [16-18]. Limits vary from 25 mg/dl (AAP), 0.5% v/v (FDA) to 1 mg/dl (EMA) – all of these are limits for a single dose of medication. Only the EMA proposes a daily limit of ethanol ingestion of 6 mg/kg/day, thus acknowledging the potential of accumulative excipient exposure through two or more medications.

 TABLE 1

Excipients of interest.

<i>Preservatives</i>
Ethanol
Propylene glycol
Benzyl alcohol
Methyl-hydroxybenzoate ^a , methyl-paraben
Propanyl-hydroxybenzoate ^a , propyl-paraben
<i>Artificial sweeteners</i>
Acesulfame potassium ^b
Aspartame
Glycerol
Sorbitol
Polysorbate-80

a) The sodium-associated parabens included.

b) Previously acesulfame p.

 TABLE 2

Inclusion and exclusion criteria for the study population.

<i>Inclusion criteria</i>
Neonatal patients ^a : receiving ≥ 2 preparations a day
Paediatric patients ^b : receiving ≥ 3 preparations a day
Hospitalised at least once:
At either department 5021, 5023, 5024, 4144, 5054, 5061 or 5062 at Rigshospitalet
During the period 1 February 2006-14 February 2016

Exclusion criteria

> 5 yrs old

No weight information available in patient chart

a) ≤ 27 days old (gestational age).

b) 28 days-5 yrs old (gestational age).

In Denmark, no studies have yet described the extent of excipient exposure or the quantity of excipient exposure in multi-medicated neonatal and paediatric patients.

The purpose of this study is to quantify the amount of potentially harmful EOIs – presented in **Table 1** – administered to the multi-medicated neonatal and young paediatric patient. Further, it will identify the most vulnerable group of patients, thus possibly allowing the clinician to make appropriate decisions for a safer medication.

METHODS

The study will adopt a retrospective, observational design to describe the extent of excipient exposure in neonatal and young paediatric patients from Rigshospitalet, Copenhagen, Denmark.

Ethics approval and consent

The protocol was approved by The Board for Patient Safety, Danish Health and Medicines Authority (ID: 3-3013-1343/1/). The Board has waived the requirement for patient consent.

Furthermore, the study was approved by The Danish Data Committee (ID: BFH-2015-072 and I-Suite number: 04167).

Study selection

The study only involves patients who were treated at Rigshospitalet during the time period from 1 February 2006 to 14 February 2016.

For further inclusion and exclusion criteria, see **Table 2**.

Data collection

Data will be collected in the course of a journal audit including > 1,000 patients meeting the inclusion criteria and not complying with any of the exclusion criteria. Patients are identified through admission to a neonatal or paediatric unit, but may also be included if treated in an adult department on the day of inclusion. The day of inclusion is set to the day the neonate or child is administered the highest number of unique preparations.

The following information will be collected:

- Danish civil registration (CPR) number
- Gestational age
- Postmenstrual age (if different from gestational age)
- Weight (and whether actual or adjusted medical weight is stated, e.g. due to overhydration)
- Pregnancy and birth history
- Treated at neonatal, paediatric or adult department
- Diagnosis (by the International Classification of Diseases, 10th edition (ICD-10))

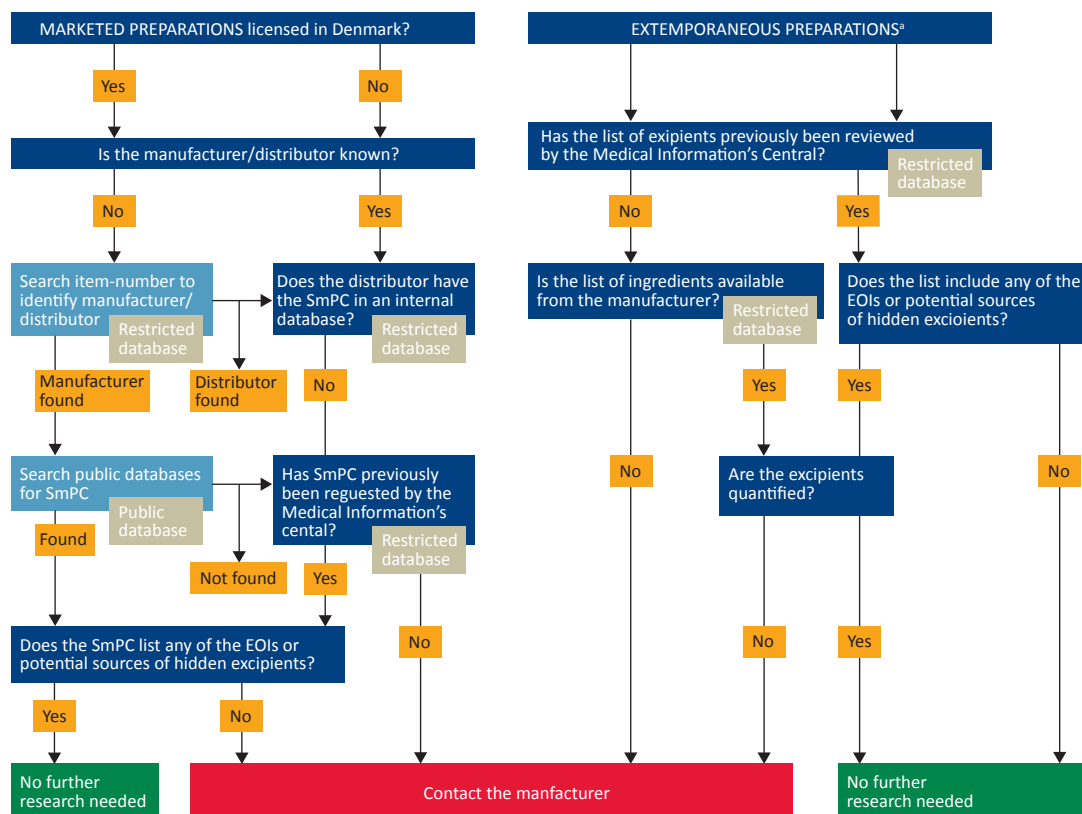
 FIGURE 1


Illustration of the process of excipient identification and quantification. EOI = excipient of interest; SmPC = summary of product characteristics. a) Includes both preparations originating from community pharmacies (Skanderborg and Glostrup) and preparations originating local hospital pharmacies.

- Daily medication:
 - Indication
 - Preparation
 - Prescription (off-label/on-label/extemporaneous)
 - Amount
 - Dose
 - Interval
 - Formulation
 - Route of administration.

The patients will be grouped according to the International Conference on Harmonization's (ICH E11) guidelines on "Clinical Investigation of Medicinal Products in the Paediatric Population":

- 0-27 days (term and pre-term)
- 28 days-23 months
- 2-11 years (please note that patients older than five years are excluded, see exclusion criteria).

Excipient identification process

After the data collection, the excipients in each drug will be identified through leaflets, monographies via Medicin-Info BFH or by direct contact to the pharmaceutical

companies and manufacturers. Depending on origin, the process of excipient quantification differs (see **Figure 1**). The concentration of each EOI will be noted.

Each drug administered will be grouped according to excipient contained, type of formulation and Anatomical Therapeutic Chemical (ATC) level 1.xxx

For all patients, accumulative daily amounts of the EOIs will be calculated based on the collected data (patient weight, drug dose and drug interval) and the information obtained during the process of excipient identification and subsequent quantification. The concentrations of ethanol and propylene glycol (the latter being one third as intoxicating as ethanol) will be combined to calculate the blood-alcohol-content (g/dl).

Statistical analysis

By parametric statistical analysis, the study will identify the frequency and mean of each excipient. All excipient exposures will be compared parametrically with clinically relevant data to establish if the amount is clinically significant. The number of patients with an exposure rate above clinically significant baselines will be noted.

We will describe the pattern of excipient exposure in preparations administered at neonatal, paediatric and

 TABLE 3

Pilot examination of monographs of 85 oral solutions^a.

Excipient	Contained in preparations	Frequency of excipient
Ethanol	Methadon SAD	13
	Methadon, non-SAD	
	Fenemal	
	Trileptal	
	Sulfametoxazol	
	Mycostatin, 100,000 IE/ml	
	Mycostatin, 100,000 IE/ml ^b	
	Digoxin	
	Zofran	
	Dexofan	
	Glycifer	
	Potassium chloride	
	Sandimmun Neoral	
Propylene glycol	Paracetamol	12
	Bonyl	
	Fenemal	
	Tegretol	
	Trileptal	
	Valcyte	
	Aerius	
	Digoxin	
	Ritrovil	
	Chloralhydrat	
	Ursofalk	
Sandimmun Neoral		
Benzyl alcohol	Dalacin	1
Acesulfame potassium	Levetiracetam	5
	Keppra	
	Zinnat	
	Fucidin	
	Phenergan	
Aspartame	Zinnat	5
	Azithromycin Stada	
	Xaluprine	
	Zofran	
	Cellcept, Orifarm	
Glycerol	Paracetamol	13
	Bonyl	
	Levetiracetam	
	Keppra	
	Zovir, 40 mg/ml	
	Zovir, 80 mg/ml	
	Sulfametoxazol	
	Esimeprazol	
	Retrovir	
	Mycostatin, 100.000 IE/ml	
	Mycostatin, 100.000 IE/ml ^b	
	Noxafil	
	Chloralhydrate	

a) The examination of the monographs did not take into account oral solutions containing benzoates, sorbitol or polysorbate-80; b) Mycostatin 100,000 IE/ml is counted twice due to different parallel importers with different package sizes.

Outcome measurements

The primary outcome is the identification of the average amount of each excipient (listed in Table 1) administered secondary to medication.

Secondary outcomes include:

- Identifying the most frequently used of the included excipients
- Calculating an average of each excipient to which each main group and subgroup was exposed
- Description of the pattern of excipient exposure for patients admitted to a neonatal unit compared with a paediatric unit and with an adult unit
- Contribution to a risk/benefit assessment of the current medication standards of the paediatric population.

Funding statements

The study has received grants from the Bispebjerg and Frederiksberg Hospitals' Research Foundation and the Danish Council for Independent Research (Grant-ID: DFF – 6110-00266). Neither these nor any future funders will have any influence on the data collection, analysis, interpretation and decision to publish.

DISCUSSION

Preservatives and artificial sweeteners used as excipients may cause harm to the exposed neonatal and paediatric patients. Three decades ago, a detailed review was performed of the medical records of all babies weighing less than 1,250 g at birth admitted to a neonatal intensive care unit. The study aimed to assess the true impact of benzyl alcohol toxicity after the use of solutions containing benzyl alcohol to flush intravascular catheters was discontinued. The study found a significant decrease in both the mortality rate (from 80.7% to 45.7%) and in the incidence of grade III/IV intraventricular haemorrhage (from 46% to 19%) among infants weighing less than 1,000 g at birth who did not receive the preservative compared with those who did [5]. Today, the EMA states that any medication containing benzyl alcohol "must not be given to premature babies and neonates" [19, 20]. A similar approach could be taken to other controversial excipients such as ethanol, but before proposing such regulations it is important to evaluate the harmful potential of the total ethanol exposure in the vulnerable neonates and young children.

In the present study, medication administered to patients up to five years of age will be examined to assess the excipient exposure during the most vulnerable maturing period of the central nervous system.

In 2015, we examined the monographs of 85 oral solutions (ATC level 7) prescribed during 2014 at one or several children's units at Rigshospitalet, Copenhagen,

adult departments. *p*-values < 0.05 are considered significant.

Denmark (see **Table 3**). The oral solutions were both of marketed and extemporaneous origin. Among the oral solutions, we found that 34 different drug preparations (40%) contained at least one of the excipients included herein. Ethanol, propylene glycol and glycerol were found with the highest frequency (at 13, 12 and 13 respectively – see Table 3). Only one drug contained benzyl alcohol. This preview does not provide information on the poly-medicated patient, who is at risk of being exposed to significant amounts of the same excipient from multiple drugs, but it emphasises the need for an examination of patient-level excipient exposure. To this day, there is an ongoing discussion of excipients in neonatal and paediatric marketed and extemporaneous drugs. Patients included in this study originate from a highly specialised hospital and thus may both represent children requiring specialist treatment and the typical neonatal or young paediatric patient. Thus, results will reflect the use of both specialist preparations and the most commonly used preparations. The prevalence of each excipient may differ from the one that would have been observed if the study had been conducted at a general hospital. Several studies have stated that

younger patients are exposed to harmful and/or potentially harmful excipients such as parabens, aspartame, etc. [2, 3, 5, 8]. None of these studies aspire to quantifying the exact amount of excipients administered to the poly-medicated patient through drugs.

In order to perform a proper risk/benefit assessment of the current medication standard, it is necessary to compare the daily quantity of excipients in the most vulnerable patient to clinically established safety levels for the same age group. The SEEN project is relevant both nationally and internationally as it will reveal the current status of excipients (frequency and amount) in medicines administered to neonates and young children.

Perspectives

The SEEN project will contribute to a discussion of the current medication standards and the use of off-licensed and extemporaneous drugs in neonatal and paediatric hospital units in Denmark and internationally. It is our hope that this will facilitate clinical research by covering aspects related to e.g., the safety, efficacy, dosing and formulations currently most used in this vulnerable group.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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