NPPG
Neonatal & Paediatric Pharmacists Group

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Exciting project to create a national standard for the administration of infusions
http://ow.ly/QBUm303nQl2

Project aims to establish a national standard for the administration of commonly prescribed medication infusions.

The problem
Weight based dosing & dilution of continuously infused medications is error prone, inaccurate, and inefficient

Aims

- Agree standardised infusion concentrations for a core set of the 20 most commonly infused drugs in neonates, children & young people.
- Standardised approach to paediatric drug infusions across UK
- Reduced prescribing errors
- Reduced administration errors

Acetaminophen versus ibuprofen in young children with mild persistent
asthma http://www.nejm.org/doi/full/10.1056/NEJMoa1515990 …

Neorecormon

Roche have recently proposed some changes to their NeoRecormon range of products including the discontinuation of the 500 unit syringe and the removal of the full dose and graduation markings from the barrels of all other syringe sizes. This was highlighted to NPPG by Andrew Wignall and a response written to Roche outlining our concerns about the impact this would have on paediatric patients, in particular neonates where no other suitable alternative exists. Our lobbying was successful and the proposed changes will not be made.

This is a very important role for NPPG. If you come across other similar issues please let us know and we'll see what we can do.

Excipients in medicines for children

Background

The European Commission introduced the Paediatric Regulation in 2007 with the aim "to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations" (1).
Numerous medicinal products routinely used to treat the paediatric population have not been studied or authorised for paediatric use, denoting widespread unlicensed and 'off-label' use of adult medicines. Excipients evaluated for safety in adult formulations may not be appropriate for paediatric patients, leading to potential adverse effects (2). Formulations must therefore be carefully selected for use in children as they may not be able to metabolise or eliminate an excipient in the same way as an adult, due to physiological and developmental differences (2). Preterm, low-birth weight neonates and infants are particularly vulnerable due to the immaturity of their hepatic and renal systems for metabolism and elimination (2).

Lack of data regarding neonatal exposure to excipients and concerns about safety prompted a group of researchers across Europe to set up the European Study for Neonatal Excipient Exposure (ESNEE) research initiative (3). It aims to "develop a platform for the systemic assessment of excipients in neonates" via a 4-step programme, with the latter "integrating the work of the other steps into a systemic assessment of safety for each excipient" (3-4). Information will be displayed as monographs comprising a summary of what is known about each excipient in the neonatal population, targeted at doctors, nurses and pharmacists (5).

Additionally, to improve the availability and access to information on excipients, the United States and the European Union Paediatric Formulation Initiatives have collaborated to create the STEP (Safety and Toxicity of Excipients for Paediatrics) database (6). Safety and toxicity information of excipients is presented in a freely accessible source, including preclinical, clinical, regulatory information and toxicological reviews (6).

Excipients are essential components of drug formulations, facilitating their manufacture and storage (4). However, some have safety concerns in children such as those listed in Table 1. The list includes all prioritised excipients included in the STEP pilot database and in the ESNEE project (3, 6). Exposure to these excipients should be minimised as much as possible, though use of certain excipients may be justified in terms of risk-benefit balance. Unfortunately, lack of information on excipient amounts in a medicine's Summary of Product Characteristics (SPC) makes assessment of the associated risks difficult for Healthcare Professionals.

The list is intended to highlight potential issues associated with excipients. It is not exhaustive and exclusion does not indicate safety.

Table 1: Examples of problem excipients and their safety concerns

Excipient	Main safety concerns
Propylene glycol	Central Nervous System (CNS) effects, especially in neonates and children under 4 years (7)
Ethanol	Intoxication (3,7)
Polyoxyl castor oil	Severe anaphylactoid reactions (8)
Polysorbate 80	E-Ferol syndrome (2), hypersensitivity reactions (9)
Benzyl alcohol	"Gasping syndrome" in neonates (11)
Benzoic acid / sodium benzoate	Jaundice in neonates (7,12)
Parabens (methyl- and propyl- hydroxybenzoate)	Suggestion of oestrogenic activity with potential reproductive effects (with propylparaben) (3,13), hypersensitivity reactions (14), hyperbilirubinaemia in neonates (15)
Benzalkonium chloride	Bronchospasm from anti-asthmatic drugs (16-17)
Sodium metasulfites	Wheezing, dyspnoea and chest tightness in asthmatic children (17)
Sorbitol	Osmotic diarrhoea and gastrointestinal discomfort (18-19)
Glucose and sucrose	Obesity and tooth decay (2)
Saccharin	Hypersensitivity and photosensitivity reactions (14,20)
Aspartame	A source of phenylalanine in patients with phenylketonuria (2,7)
Colouring agents	Sensitivity reactions and hyperactive behaviour in children (14)

Solvents

Propylene glycol

Propylene glycol (PG) is a solvent used in a variety of oral liquid, topical and injectable medicines (7). Intravenous formulations may contain between 20% and 80% PG, for example, lorazepam (80%), phenobarbital (70%), diazepam (40%) and phenytoin (40%) (21).

PG is known to be particularly toxic in some patients that are unable to adequately metabolise and eliminate the excipient e.g. in neonates, young children and in those with renal failure (8, 22). Paediatric patients below the age of 4 years have a limited metabolic pathway (alcohol dehydrogenase) and neonates have a longer elimination half-life than adults therefore accumulation of PG can occur (7). Depression of the CNS is its main toxic action (7). At high doses and in at-risk patients, hepatic or renal impairment, seizures, intravascular haemolysis, arrhythmia, lactic acidosis, respiratory depression and hyperosmolality have been reported (14, 22). Toxicity may be increased when co-administered with any substrate of alcohol dehydrogenase such as ethanol (22).

Despite published clinical data demonstrating that higher PG load may be safely administered to children above 4 years of age and adults, no firm recommendations on a safe dose of PG can be made for the paediatric population (23). A more cautious approach is still recommended for children under 5 years due to lack of clinical data (23). See Table 2 below for the European Medicines Agency (EMA) proposed safety limits for PG in children.

Table 2: EMA proposed safety limits for PG (23)

	Neonates up to 28 days (or 44 weeks post-menstrual age for pre-terms)	1 month - 4 years	5 - 17 years
Safety limits (max. daily dose)	1mg/kg	50mg/kg	500mg/kg

Calculating quantity of PG in a pharmaceutical product in % w/v
Some pharmaceutical companies state quantity of PG in mL/5mL of product. The concentration in % v/v can be converted to % w/v using the specific gravity of PG, which is 1.036 (i.e. 1mL weighs 1.036g) (24). For example, a PG concentration of 3% v/v corresponds to 3.1% w/v (3mL/100mL x 1.036 = 3.1g/100mL).

Ethanol

Ethanol is widely used as a solvent in oral liquid formulations. Concerns associated with its use in children include risk of acute intoxication with accidental overdose and chronic toxicity with long-term use (7). Children, especially those under 6 years of age, are more vulnerable to the effects of alcohol which may include drowsiness, behavioural changes, and impaired ability to concentrate and participate in school activities (25). In 1984, the American Academy of Paediatrics set an arbitrary blood alcohol concentration (BAC) of 25mg/100mL that should not be exceeded after a single dose of an alcohol-containing medicine (26). The US Food and Drug Administration subsequently set a maximum limit of ≤0.5%, 5% and 10% ethanol in oral products intended for children <6 years, children 6-12 and children >12 years, respectively (2).
In January 2014, the EMA proposed more detailed information on alcohol content in patient information leaflets (PILs) as well as alcohol content thresholds of different age groups in a draft for the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' which is yet to be published (25,27). See Table 3 below:

Table 3: EMA proposed safety thresholds for ethanol in children ≤12 years (25).

	Children <6 years	Children 6-12 years
EMA Proposed ethanol thresholds in paediatric population	BAC level should not exceed 1mg/100mL (a dose of 6mg/kg)	BAC levels should not exceed 12.5mg/100mL (a dose of 75mg/kg)

Calculating quantity of ethanol in a pharmaceutical product (in % w/v)
In the UK, information on ethanol content of a medicine can be found in the PIL or the SPC. The concentration in % v/v can be converted to % w/v using the specific gravity of ethanol (alcohol), which is 0.789 (0.8 can be used as an approximation) (25). For example, an ethanol (alcohol) concentration of 12.5% v/v corresponds to 10% w/v (12.5mL/100mL x 0.8 = 10g/100mL)
Theoretical calculation of BAC (based on ref 25):

$$BAC\ (g/L) = \frac{ingested\ ethanol\ in\ a\ single\ dose\ (g)}{volume\ of\ distribution\ (L/kg)\ x\ weight\ (kg)}$$

(volume of distribution (L/kg) should be assumed to be 0.6)

The BAC in g/L can then be converted to mg/100mL or mg/dL for interpretation with the safety thresholds in table 3.

Vehicle

Polyoxyl castor oil

Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions (8, 28).

Solubilising agent

Polysorbate 80

Polysorbates are widely used as solubilising agents (2) in oral, parenteral and topical pharmaceutical formulations and are generally regarded as non-toxic and non-irritant materials (9). However, serious adverse effects (thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis) have been reported in low birth weight infants after receiving a vitamin E preparation containing a mixture of polysorbates 20 and 80, known as E-Ferol syndrome (2,9). Hypersensitivity reactions, usually delayed, have also been reported following exposure to pharmaceutical products containing polysorbate 80 in some individuals (10).

Preservatives

Benzyl alcohol

Benzoic acid, sodium benzoate and benzyl alcohol (which is metabolised to benzoic acid) are used as preservatives in a variety pharmaceutical formulations (2).

Benzyl alcohol is highly toxic to neonates, particularly with parenteral administration to low birth weight neonates (29). Intravenous (IV) administration of very small quantities (the benzyl alcohol present as a preservative in a saline flush for IV lines) has been associated with serious adverse events and death in neonates (29). Toxicity is characterised by CNS depression, metabolic acidosis, gasping respirations, cardiovascular failure and haematological anomalies ("gasping syndrome") (11). Toxicity has been attributed to the accumulation of benzoic acid due to the immaturity of metabolic enzymes in this age group (11).

Benzoic acid/benzoates

Benzoic acid has the ability to displace bilirubin from albumin, leading to hyperbilirubinaemia (12). Increase in bilirubinaemia following parenteral administration of benzoic acid or benzoates may increase jaundice in pre-term and full-term jaundiced neonates, which may develop into kernicterus (bilirubin induced brain dysfunction) (12). Benzoic acid and benzoates must therefore be used with caution in this population.

Parenteral preparations containing benzyl alcohol should not be used in neonates unless strictly necessary (8). The same precautions should be applied to parenteral preparations containing benzoic acid or sodium benzoate (30).

The World Health Organisation (WHO) has set a group acceptable daily intake (ADI) of 0-5mg/kg/day for benzoic acid, the benzoates and benzyl alcohol in adults, but specific ADI in the paediatric population is unknown (18). Current recommendations contra-indicate benzyl alcohol for children up to 3 years of age (e.g. amiodarone injection contraindicated in children <3 years) (11, 31). While recommendations remain unchanged in neonates, the EMA propose in a draft for the guideline 'Excipients in the label and package leaflet of medicinal products for human use' that benzyl alcohol may be used with caution in children >4 weeks (11).

Parabens (methyl-, ethyl- and propyl-hydroxybenzoate)

Parabens are used as antimicrobial preservatives in pharmaceutical products (2). Methyl and propylparabens are included in gentamicin injection, which has been widely used in neonates (30). They are generally safe although should be avoided as much as possible in critically ill neonates with jaundice, kernicterus and hyperbilirubinaemia as their metabolism and excretion pathways could cause displacement of bilirubin from albumin and accumulation in the body (2,30).

Concerns have been raised in the past decade of possible disruption of endocrine systems with the use of parabens (13). The EMA has addressed these concerns in a recent reflection paper on the use of methyl- and propylparabens as excipients in human medicinal products for oral use (13). The EMA concluded that methylparaben, used as a pharmaceutical excipient within the recommended effective concentrations as a preservative, is considered safe for children of all ages (13). A permitted daily exposure of 2mg/kg/day (based on results on the female reproductive system) has been calculated for propylparaben, which applies to all adults and paediatric patients (13).

Benzalkonium chloride

When used as a preservative in nebulised solutions of anti-asthmatic agents, benzalkonium chloride has been reported to cause dose-related bronchoconstriction (16). Anti-asthma products should not be preserved with benzalkonium chloride (30).

Antioxidant

Sodium metasulfites

Sodium metasulfites are used as antioxidant preservatives in oral formulations (2). They are odourless and tasteless and thought to be non-toxic (2). However, sodium metabisulfites have been associated with hypersensitivity reactions and bronchospasm (28), particularly in asthmatics (32). In view of wheezing, dyspnoea and chest tightness observed in asthmatic patients, sulfites should be avoided in these susceptible patients (17).

Sweetening agents

Sucrose and glucose

Sucrose is calorific and can contribute to obesity in a poorly managed diet (2). Sugar-free preparations should be used whenever possible, particularly if the medicine is being given long-term due to the added risk of dental caries (8). If unavoidable, dental hygiene measures should be advised including rinsing the mouth after taking a formulation containing sugar, especially after intake of viscous formulations that may have a prolonged contact time in the oral cavity (2). Formulations containing high amounts of sugar should be avoided in diabetic patients as well as those suffering from hereditary fructose intolerance (HFI) (7).

Sorbitol

Sorbitol is a sugar alcohol used as a vehicle and stabiliser in oral liquid formulations, in addition to its role as a sweetener (18). Preparations containing sugar alcohols are marketed as "sugar-free" since they do not cause dental caries (8). As they are absorbed more slowly than conventional sugars, sugar alcohols are considered suitable for diabetic patients (18). Common adverse effects associated with sorbitol are osmotic diarrhoea and gastrointestinal discomfort (18, 19). Limited data are available on the relevant thresholds of polyols (e.g. sorbitol, mannitol) in children (1) though an oral dose of greater than 140mg/kg/day may result in gastrointestinal symptoms (19). Sorbitol is metabolised to fructose therefore is unsuitable for those with HFI (2).

Artificial sweeteners

Artificial sweeteners are low-calorie or calorie-free, non-cariogenic, and within the ADI, considered safe for consumption by diabetic patients (33). They are used to increase palatability and to mask unpleasant taste (2). The use of sweeteners is prohibited in foods for infants and young children (< 3 years) though they are present in a number of medicines licensed for these age groups (33-34). The evidence-base shows that artificial sweeteners are considered safe to consume up to the ADI in the general population, with the exception of foods for infants and young children (33).

Saccharin

Saccharin, a synthetic sweetening agent, is commonly used in the pharmaceutical industry in the manufacture of both solid and liquid dosage forms (17). There have been rare reports of hypersensitivity reactions (mainly dermatologic) and photosensitivity reactions with saccharin (14). Cross reactions between saccharin and sulphonamides have been demonstrated therefore it should be avoided in children with sulphonamide allergy (17).The group ADI for saccharin and its salts is 0-5mg/kg (35).

Aspartame

The artificial sweetener aspartame is the methyl ester of two amino acids – aspartic acid and phenylalanine (2). Aspartame should be avoided in children affected by phenylketonuria, and is contraindicated in homozygous autosomal recessive patients (7). Additionally, cross-reactivity with sulphonamides can occur (7). An ADI of 0-40mg/kg has been established by the European Food Safety Authority however this value is not confirmed for infants below 12 weeks of age due to lack of data (36). Use aspartame-containing medicines with caution in this age group (36).

Colouring agents

Colouring agents are used in medicinal preparations to improve acceptability to patients, to aid identification and prevent counterfeiting (14). They are also used to increase the stability of light-sensitive drugs (14). Their use in paediatric preparations must be justified in terms of the necessity to colour the preparation and the selection of a particular colouring agent (1). Most colouring agents used in pharmaceutical oral formulations belong to one of the following groups: azo dyes (e.g. tartrazine, sunset yellow), quinoline dyes (e.g. quinoline yellow), triphenylmethane dyes (e.g. FD&C blue) and xanthene dues (e.g. erythrosine) (7). The use of artificial colours in foods for infants and young children is prohibited by the European Union; this complete ban does not apply to medicines (34).

Colouring agents are not recommended in the paediatric population as many artificial agents have been associated with adverse effects including hypersensitivity, gastrointestinal intolerance, dermatological reactions and carcinogenicity (2, 17). The European Food Safety Authority's (EFSA) scientific panel on additives, lowered the Acceptable Daily Intakes (ADIs) for the artificial food colourings Quinoline Yellow (E104), Sunset Yellow (E110) and Ponceau 4R (E124) (37). The European Commission asked EFSA to consider these colours after a study was published by Southampton University (38) linking certain mixtures of these colours and the preservative sodium benzoate with hyperactivity in children. The ADI's are reported to have been reduced for different reasons in each case with the available data from the Southampton study not thought to substantiate a causal link between colours and possible behavioural effects. ADI values are presented by the Joint FAO/WHO Expert Committees on Food Additives (JECFA) – see Table 4 below (35).

Table 4: ADI for 6 artificial colours included in the McCann et al (2007) study (38)

Colouring agent	ADI
Sunset yellow FCF (E110)	0-4mg/kg
Quinoline yellow (E104)	0-5mg/kg
Carmoisine (E122)	0-4mg/kg
Allura red (E129)	0-7mg/kg
Tartrazine (E102)	0-7.5mg/kg
Ponceau 4R (E124)	0-4mg/kg

Summary

Despite the new paediatric regulation, children are still being exposed to potentially harmful excipients (39). A list of excipients in a medicinal product can be found in the manufacturer's PIL or SPC but amounts are rarely specified. Quantitative information is essential for pharmacists and other healthcare professionals to take into account potential excipient issues when selecting medicines for the paediatric population. Additionally, acceptable daily intakes for the paediatric population needs to be defined to aid decision making and to monitor for any adverse effects if the benefit of a medicine is deemed to outweighs the risks.

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- This document is believed to reflect the medical literature at the time of writing.

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