

Paracetamol Syrups and Propylene Glycol Exposure in Children: A Reflection on the Current Belgian Context

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Keywords

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Abstract

Dafalgan Pédiatrique/Dafalgan Kind recently adapted its syrup. This new formulation contains propylene glycol as excipient, as mentioned in the product information in accordance with the European Commission guideline (> 1 mg/kg/day in neonates). The guideline's thresholds relate to the specific information that should appear in the package leaflet, not similar to safety thresholds. There is a 28-fold difference in propylene glycol exposure between both currently marketed products (Dafalgan versus Perdolan, 7 versus 293.5 mg/kg/day), so that there is an opportunity to limit exposure below clinical relevance, without full avoidance. The current knowledge on propylene glycol in children is summarized

Introduction

Paracetamol (acetaminophen) is the most commonly used medicine in humans, also in children, infants and neonates. Paracetamol is an over the counter (OTC) medicine in Belgium, be it commonly supported by advice of health care providers, like paediatricians or pharmacists (1). Recently, Dafalgan Pédiatrique/Dafalgan Kind adapted its formulation so that this new formulation contains propylene glycol as an excipient as mentioned in the summary of product characteristics (SmpC) (2,3). Excipients, including alcohols like propylene glycol are commonly added to formulations to ensure stability and quality of a given formulation over a given shelf life ('expiration date'). Alcohols are hereby typically used as solvent for either the active pharmaceutical ingredient, or related to the flavouring, commonly to improve solubility in liquids or water. This means that propylene glycol is not unique to syrups, but can also be present in e.g. intravenous formulations like phenobarbital, digoxin, lorazepam or esmolol vials. This co-solvent has a consistent history of use in various formulations and also food, as has a GRAS (generally regarded as safe) status. For healthcare providers involved in the care of children, there is relevance to consider this switch

since - similar to ethanol - the elimination capacity of propylene glycol like any other alcohol is limited, since metabolized by alcohol dehydrogenase (ADH to lactaldehyde, subsequently by aldehyde dehydrogenase to lactate), or (minor route) by primary renal elimination. Although propylene glycol is usually considered innocuous, in larger quantities it can cause metabolic perturbations like lactic acidosis and hyperosmolality. In the event of overexposure, toxicity may occur, related to accumulation, changes in osmolar gap, kidney or hepatic impairment, with subsequent clinical signs like central nervous system depression (4). Other side effects such as haemolysis, mental status changes or renal toxicity (e.g. renal tubular acidosis, acute tubular necrosis) have been reported as manifestations of propylene glycol toxicity. Case series on intoxication have been described, mainly related to continuous intravenous lorazepam administration in adult and paediatric ICU settings. Specific for infants and neonates, the likelihood of propylene glycol accumulation is proportionally (/kg) higher because of their lower clearance capacity (lower ADH activity and lower renal elimination). Historically, MacDonald et al. reported on the increased incidence of seizures (33 % instead of 11 %), renal failure, increased direct bilirubinaemia following a change in the daily volume

TABLE 1: Overview of the product names with the amount of propylene glycol/ml, indications, registered population, recommended and maximum daily dose and the related propylene glycol exposure (9).

Product name	Indication	Paediatric population	Recommended dose	Maximum dose, and propylene glycol exposure
Perdolan Enfants/kinderen 32 mg/ml 104,8 mg/mL propylene glycol*	Pain Fever	<50 kg	15 mg/kg every 4 h	60 mg/kg/day 196.5 mg/kg/day
Dafalgan Pédiatrique/Kind 30 mg/ml 3,5 mg/mL propylene glycol*	Pain Fever	Authorized: From 3-16 kg (approx. from birth to 4 years)	15 mg/kg every 6 h	60 mg/kg/day 7 mg/kg/day
Paracetamol Teva 40 mg/ml no propylene glycol**	Mild to moderate pain Fever	From 3 months	10 mg/kg every 4 h 15 mg/kg every 6 h	60 mg/kg/day no exposure
Perdolan 50 mg/ml 1,94 mg/mL propylene glycol **	Pain Fever	From 1 year (>10 kg)	15 mg/kg every 4 h	60 mg/kg/day 2.1 mg/kg/day
* = commercialized in Belgium at present; ** = not commercialized in Belgium at present.				

of intravenous multivitamin administration (with PG as the solvent) from 1 ml/day to 10 ml/day in very low birth weight infants (5). This multivitamin solution for intravenous administration contained 300 mg propylene glycol/ml solution. Therefore, the change in the daily volume administered resulted in an increase of exposure of 300 mg/day to 3 000 mg/day (equal to at least 200 mg/kg versus 2 000 mg/kg/day) and patients were treated with this solution for at least 14 days. The ‘Kaletra syrup (lopinavir/ritonavir)’ observation serves as the most recent observation on the clinical relevance, be it following co-exposure to ethanol and propylene glycol (42.4% ethanol, 15.3% propylene glycol). Because of case series in neonates, the Food and Drug Agency send out a black box warning and adapted the label so that the drug should not be administrated to any neonate <42 weeks of postmenstrual age and <2 weeks postnatal age) (6). However, there are also data that short term lower propylene glycol exposure (25-50 mg/kg/day) was tolerated well in preterm and term neonates (7). The same situation applies to the EU market. Because of the relevance of excipient toxicity and the potential for clinical adverse events, a European Commission guideline has been developed with warning statements when certain excipients in medicinal products are present above defined thresholds. These thresholds are intended to determine when information or warnings should be included in the product information; they do not represent absolute safety limits, nor do they imply that products exceeding them are inherently unsafe (8). Rather, the acceptability of excipient exposure must be considered in the context of the overall benefit-risk balance of the medicinal product. The assessment report for propylene glycol also states that “it should be kept in mind that higher doses of propylene glycol may be administered, when justified on a case by case basis in order to support the safety of the proposed formulation, and were suggested in the absence of

compelling data”. “Clinical data showed that in children from the age of 5 years and adult patients, up to 500 mg/kg/day of propylene glycol could generally be considered safe. In the absence of compelling data this safety threshold is decreased to 50 mg/kg/day in children <5 years old, and even to 1 mg/kg/day in (pre) term neonates due to known immaturity of both metabolic and renal clearances of propylene glycol in these populations” (8).

Objectives

Provide an overview on the currently registered and marketed paracetamol syrup formulations for children in Belgium, provide a /kg based calculation of related propylene glycol exposure, applying the registered doses, and bring perspective and provide context related to the existing recommendations of the European Medicines Agency on propylene glycol use in formulations (8).

Methods

The medicinal product database for human use of the Belgian agency was searched for the currently registered and marketed formulations on the Belgian market (9). Based to the specific SmpC on dosing and propylene glycol concentrations, the propylene glycol exposure /kg was calculated.

Results

In Belgium, there are 4 liquid paracetamol formulations registered. However, 2/4 are at present not marketed (Paracetamol Teva 40 mg/ml, Perdolan 50 mg/ml) in Belgium. The product names with the amount of propylene glycol/ml, indications, registered population, recommended and maximum daily dose and the related propylene glycol exposure are listed in Table 1.

Conclusion

'Perfect is the enemy of good'
(*'le mieux est l'ennemi du bien'*)

Propylene glycol exposure is for sure a potential relevant issue, with potential severe or serious adverse reactions, as reported in adults, children, infants and neonates (4-8). Consequently, and as a precautionary measure, labelling guidelines with age-based thresholds to report on in the SmpC have rightfully been implemented (9). This provides us with the opportunity to identify, quantify, and prevent or mitigate propylene glycol overexposure. It also results in transparency in the event of polypharmacy with different sources of alcohols as excipient. For paracetamol syrups - and considering the current marketed products - there is a 28-fold difference in propylene glycol exposure between both currently marketed products (Table 1), so that there is an opportunity to limit (7 mg/kg/day) by selecting the best suited formulation, but not to fully avoid exposure above the threshold to report propylene glycol in the product information. Although exposure above the labelling threshold cannot be fully avoided, a resulting exposure level (7 mg/kg/day) is considered acceptable from a clinical safety point of view, as exposure to 25-50 mg/kg/day in neonates was not associated with biochemical signs of accumulation or metabolic disturbances (7).

Conflicts of interest

Karel Allegaert is member of the Paediatric Committee (PDCO) for Belgium at the European Medicines Agency (EMA), is the representative of the European Academy of Paediatrics in the Health Care Providers Working Party of EMA, as well as member of the committee for medicines for human use, Federal Agency for Medicines and Health Products (FAMHP). This short communication reflects his personal opinion, not the opinion of the PDCO, EMA or FAMHP. His conflict of interest is in the public domain. This work has been performed without any funding.

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