

Propylene Glycol in Neonates: Never Prescribed, Frequently Administered, Hardly Evaluated

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In addition to therapeutic compounds, drug formulations routinely also contain excipients needed as co-solvents, preservatives, colorants, surfactants and/or sweeteners. The majority of these excipients that have been used for many years, and are Generally Regarded As Safe, reflected in the 'GRAS' status [1,2]. Examples of excipients are lactose, aspartame, ethanol, propylene glycol, benzyl alcohol, sorbitol, xylitol, mannitol, poly-ethylene glycol, and also propylene glycol. Propylene glycol (PG) is an unintentional, but frequently co-administered excipient together with a therapeutic compound in a formulation despite the fact that PG exposure potentially results in hyperosmolarity, lactic acidosis and renal/hepatic toxicity [3,4]. Toxicity is generally considered to be related to PG accumulation with plasma osmolar changes as first sign of potential subsequent toxicity [3,4]. Median PG clearance in non-critically ill adult patients is 15.9 l/h, and was only modestly lower (-10 %) in critically ill adults (14.6 l/h). Overall PG clearance is in part explained by primary renal elimination (glomerular filtration rate, 45%), in part by hepatic metabolism (alcohol dehydrogenase, 55%) to lactate and pyruvate [3]. However, this does not linearly apply in neonates, commonly exposed to PG.

Newborn have physiological impaired hepatic and renal elimination capacity [5,6]. This likely results in faster PG accumulation and subsequent toxicity, but the GRAS status does not consider these maturational differences [5,6]. PG toxicity in preterm neonates has even been documented (biochemical abnormalities, including hyperosmolarity, lactic acidosis, elevated creatinine and bilirubin) following exposure of to 3 000 mg/day of PG and for at least 5 days. These biochemical abnormalities were followed by clinical symptoms, including seizures and bradycardic episodes [7,8]. Although these case series go back to the 1980s, the propylene glycol example also illustrates that PG related toxicity remains important. In March 2011, The US Food and Drug Administration notified healthcare professionals of relevant health problems associated with Kaletra® (lopinavir/ritonavir) oral solution in preterm neonates [9].

This formulation indeed contains both relevant amounts of ethanol and propylene glycol. Despite these historic and contemporary reports, PG exposure in neonates is still common as quantified in a UK and a Belgian cohort [10-12], more recently confirmed in an Estonian study on excipient exposure in neonates in the absence of data on toxicokinetics and dynamics in neonates [13].

In the absence of data on tolerance and clearance, our research group initiated a PG research project in neonates to document the tolerance of low dose PG exposure and to describe PG clearance, including the differences in routes of elimination (renal compared to hepatic). In consecutive reports, we documented that a median PG exposure of 34 mg/kg/day for 48 hours did not affect the normal renal, metabolic and hepatic adaptations in postnatal life [12]. More recently, these findings were confirmed in a formulation controlled approach (paracetamol-PG compared to paracetamol-mannitol formulation tolerance) [14].

To describe maturational pharmacokinetics, we first developed a PG assay to quantify low concentrations of PG in neonatal plasma and urine in low volume samples [15]. This assay was subsequently used to quantify PG in 372 plasma samples collected from 62 (pre) term neonates exposed to PG [16]. The PG population clearance was 0.0849 l/h. Birth weight and postnatal age were both identified as relevant covariates to predict individual PG clearance [individual clearance = $0.0849 \times \{(\text{birth weight}/2.720 \text{ kg})^{1.69 \times (\text{postnatal age}/3 \text{ days})^{0.201}}\}$]. The model was subsequently used to simulate exposure to PG co-administered with therapeutic compounds like paracetamol-PG, Phenobarbital-PG or more recently, lorazepam-PG [16,17].

Besides compound specific relevance, we also encountered during the PG project some issues that are of relevance beyond the PG specific observations. These issues will be discussed together with the additional information needed on aspects of PG toxicity in neonates to further improve clinical safety. At least, we hereby illustrated the feasibility to study aspects of clinical pharmacology of excipients in neonates [18].

At present, most but not the entire Summary of Product Characteristics (SPC) leaflets mention the presence of PG as part of the formulation, but almost none mention the exact amounts used. Moreover, for a single therapeutic compound, either PG amounts differ (e.g. Phenobarbital intravenous formulation) or some contain PG while other does not contain (e.g. acetaminophen intravenous formulation) this excipient [18]. This makes PG exposure calculations in neonates almost impossible in the routine clinical setting. Secondly, on the issue of PG clearance in neonates, we published median estimates and the most important covariates (i.e. weight and postnatal age), but it is to be anticipated that other disease characteristics (e.g. liver dysfunction, renal failure, co-medication) may impact PG clearance capacity. In an attempt to improve the knowledge on the differences in routes of PG elimination between adults and neonates, we further explored the plasma dataset in combination with urine collections in these neonates and hereby observed that - compared to adults - hepatic elimination seems to be more relevant when compared to primary renal elimination [18]. Such proportional differences may be of relevance in the extrapolation of excipient-excipient interaction (e.g. PG and ethanol) or to extrapolation the impact of comorbidities in early life (e.g. hepatic compared to renal failure). Finally, another important

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assumption in our extrapolations is that there are similarities in the pharmacodynamics, i.e. that the threshold of toxicity relates to plasma osmolar changes and is not different between adults and neonates.

Consequently, focused studies on PG and other excipients in neonates remain urgently needed to avoid toxicity and to improve clinical care. The European Study for Neonatal Excipient Exposure (ESNEE research initiative), funded by the ERA-NET PRIOMEDCHILD aims to improve this knowledge, applying a systematic approach [19,20]. In a first step, the ESNEE research group aims to describe the 'epidemiology' of excipients. It is about 'setting the scene': which excipients are in use and how much of each excipient is included in medicines given to neonates. In a second step, the ESNEE program aims to determine what is at present already known on excipients in neonates. This will be based on a series of systematic reviews about neonatal excipient toxicity. The third step is to 'generate information on missing links': to quantify concentrations of key excipients in neonates. Finally, ESNEE aims to integrate this work to assess of safety for each excipient: 'back to the clinical relevance' [19,20]. Our PG research project may hereby serve as a case study to at least illustrate its feasibility [18]. This editorial hereby aimed to raise awareness of clinical toxicologists to this issue.

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