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The propylene glycol research project to illustrate the feasibility and difficulties to study toxicokinetics in neonates

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ABSTRACT

This paper aims to describe our propylene glycol (PG) research project to illustrate the feasibility and the difficulties encountered to perform excipient studies in neonates. PG is frequently co-administered excipient. PG accumulation potentially results in hyperosmolarity, lactic acidosis or hepato-renal toxicity in adults, reflecting issues related to pharmacokinetics (PKs) and -dynamics (PDs). Consequently, similar observations in neonates are urgently needed.

Since newborns display 'physiological' impaired hepatic and renal elimination capacity, description of PG PK in neonates is warranted. The PG PD was assessed based on indicators of renal, hepatic and metabolic (in)tolerance earlier reported in adults and relating to osmolar changes. Based on the PK and PD data collected in neonates, we suggest that there is a lower limit of PG tolerance in neonates.

In addition to preliminary data on PG disposition and tolerance in neonates, we mainly focus on the limitations of the current observations and the difficulties encountered during this PG project to further illustrate the specific setting of neonatal research.

1. Introduction

Although the general principles of disposition of exogenous compounds also apply in neonates, their characteristics warrant a tailored approach. History provides us with evidence on the deleterious effects of chloramphenicol (grey baby syndrome), benzyl alcohol (gasping syndrome) or dexamethasone (cerebral palsy) in neonates. Children display maturation in the disposition of exogenous compounds, and this maturation is most prominent in early life (Allegaert et al., 2008). There are age-dependent changes in body composition, almost all phases I and II metabolic processes mature while renal drug clearance in early life is low and almost completely depends on glomerular filtration rate (GFR). These changes all have impact on the pharmaco- and toxicokinetics (concentration–time curves, pharmacokinetics, PK). Besides age-dependent differences in effects, differences in side effects should also be considered (pharmacodynamics, PDs) while phenotypic variation in metabolism of exogenous compounds is based on constitutional, environmental and genetic factors, but in early life mainly reflects ontogeny (de Cock et al., 2011). As already illustrated based on the benzyl alcohol observations, a similar approach is needed for excipients, compounds that are added to ensure solubility and stability of a formulation throughout a shelf life, over a temperature range or to adapt to other external conditions.

Whittaker et al. (2009) have refocused on the exposure to additives in formulations administered to (pre)term neonates. The authors hereby described the presence of several solvents (e.g. sorbitol, ethanol, propylene glycol) in drugs administered to neonates in the absence of any data on the safety level of exposure. Similar to the established use of off-label drugs in this population, we have to be aware that we are in a setting of established administration of these (co)solvents in neonates. One of the co-solvents used is propylene glycol (PG).

Propylene glycol (1,2 propanediol) is a clear, colourless, odourless, water-soluble alcohol. Physico-chemically, it is similar to ethylene glycol but less toxic (Wilson et al., 2005; Zar et al., 2007). However, PG can cause lactic acidosis, increase in anion gap or osmolar gap, hyponatriemia or hepatic dysfunction (increase direct serum bilirubin). Other side effects such as hemolysis, mental status changes or renal toxicity (e.g. renal tubular acidosis, acute tubular necrosis resulting in increased serum creatinine and oliguria) have been reported as manifestations of PG accumulation and toxicity (Speth et al., 1987; Wilson et al., 2005; Zar et al., 2007).

Most of the reports relate to continuous intravenous administration of benzodiazepines containing PG as solvent in adult intensive care setting. About 45% is eliminated by renal route, 55% undergoes hepatic metabolisation through lactate and pyruvate (Speth et al.,

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1987). Consequently, patients with alterations in hepatic and/or renal elimination capacity are at increased risk for PG accumulation and subsequent metabolic and/or clinical symptoms. To illustrate the clinical relevance in neonates, we refer to the recent FDA drug safety communication on serious health problems in preterm neonates exposed to an oral solution of lopinavir/ritonavir (Kaletra®, Abbott Laboratories, IL, United States), containing ethanol (42.4%, v/v) and PG (15.3%, w/v). The review of the adverse event reporting system database resulted in the recommendation to avoid this formulation before both the postmenstrual age of 42 weeks and postnatal age of 2 weeks has been attained (www.fda.gov, accessed 01.08.11). This recommendation suggests that there are maturational changes in PG elimination and tolerance. However, there are no data on PG clearance estimates and its covariates in neonates at present. Taking the anticipated extensive variability in clearance and the clinical relevance into account, focused observations in neonates are needed (Allegaert et al., 2008). In addition to the absence of PK estimates, we also have to consider potential age-related, PD differences (e.g. effects on the developing central nervous system compared to the mature, adult brain) (Lau et al., 2012).

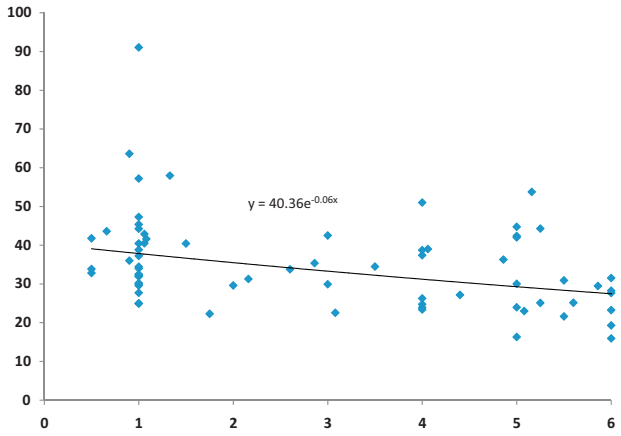

Fig. 1. 69 plasma PG observations collected in neonates following the first administration of iv paracetamol-PG (loading dose, 20 mg/kg iv paracetamol, co-administration of 16 mg/kg PG). *X*-axis: hours; *Y*-axis: PG plasma (mg/L).

2. The propylene glycol in neonates research project

As a first step of the PG project in neonates, sources of iv PG exposure in neonates were retrieved (diazepam, digoxin, diphantoin, etomidate, lorazepam, nitroglycerin, pentobarbital, phenobarbital). For ethical reasons and to improve feasibility and clinical relevance, we decided to collect observations in neonates exposed to digoxin (1656 mg PG/mg), diphantoin (8 mg PG/mg), paracetamol (0.8 mg PG/mg) or phenobarbital (3.5 mg PG/mg) since these compounds are prescribed in our neonatal intensive care unit. This approach enabled us to study PG disposition in neonates exposed to PG during clinical care. Obviously, this also means that neonates potentially were exposed to different PG sources. An unanticipated problem was that although PG was mentioned on the SPC, there was no routine report on the concentration and there were differences between formulations of the same compound (e.g. phenobarbital, up to 130 mg PG/mL).

In a second step, a PG assay was developed (Kulo et al., 2011). Neonates display extensive variability in metabolic and renal elimination clearance (Allegaert et al., 2008). Since PG is eliminated by hepatic (alcohol dehydrogenase) metabolism and primary renal elimination, we aimed to quantify PG in low volume plasma and urine samples. To illustrate the feasibility, PG time–concentration plasma observations as collected in neonates following iv paracetamol loading dose (20 mg/kg, equal to 16 mg/kg PG, PARANEO study) administration are provided (Allegaert et al., 2011; Kulo et al., 2011). Based on 69 PG plasma measurements following 16 mg/kg PG administration, peak PG concentrations were about 40 mg/L, through concentration 6 h later were 20–30 mg/L. Assuming a one-compartment model, a distribution volume of 0.5 L/kg and an elimination half life of 6–12 h can be estimated (Fig. 1). Simultaneously, in cases with a bladder catheter, urine was collected in the first 6 and 24 h time interval following initiation of paracetamol-PG administration. If we focus on urine collections following the loading dose, the median relative contribution of primary renal elimination to overall PG exposure was 7 (range 1–37) %. When further extended to the first 24 h during repeated iv paracetamol-PG exposure (median PG exposure 40 mg/kg), this increased to 15 (range 7.8–78) %. It seems that postmenstrual age is one of the covariates of PG renal elimination, but somewhat different to what we initially anticipated. A lower PMA resulted in a proportionally higher renal elimination of PG (Fig. 2). This might reflect either a difference in ontogeny between alcohol dehydrogenase and primary renal elimination in favour of primary renal elimination, or might reflect differences in renal tubular transport (Allegaert et al., 2008; Shehab et al., 2009). To further explore covariates of PG disposition in neonates, we combined the PG dataset following iv paracetamol-PG with datasets collected following iv phenobarbital-PG and digoxin-PG exposure in a pooled pharmacokinetic analysis (De Cock et al., 2012). Non-linear mixed effect modelling is the preferred tool since this allows the analysis of sparse and unbalanced datasets. Additionally, it permits exploration of different covariates (e.g. body weight, age, renal function) to explain variability (de Cock et al., 2011; Knibbe and Danhof, 2011).

Finally, renal (creatinine, diuresis), hepatic (ALT, AST, gamma GT) and metabolic tolerance (lactate, bicarbonate, base excess, sodium) before, during and following PG exposure in neonates was assessed. These indicators of PG related toxicity were based on indicators earlier reported in literature. The reported dataset on 5566 observations prospectively collected in 69 neonates before, during or following a median PG exposure of 34 (range 14–252) mg/kg/24 h has been further extended with 20 additional cases included in the PARANEO study (Allegaert et al., 2010, 2011). In essence, progressive postnatal adaptation in renal, metabolic and hepatic function was confirmed, unrelated to the PG exposure.

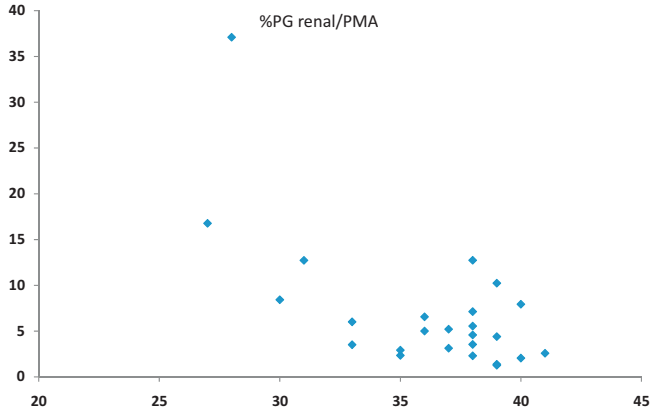

Fig. 2. Median PG (retrieved/exposed) in urine collections of 18 neonates is 15 (range 7.8–78) %. There is a higher retrieval (%) in more immature neonates. *X*-axis = postmenstrual age (PMA, weeks); *Y*-axis = % PG (retrieved/exposed).

Table 1
Specific issues encountered during the PG project that are of relevance beyond compound specific observations to study excipients in neonates.

Does a given formulation contain PG and – if so – what is the amount of exposure?
Most of the SPC's mention the presence of PG as part of the formulation, but are unclear about the amount used. Even for one specific compound (e.g. intravenous phenobarbital), there are different formulations with different amounts of PG and/or ethanol
The need for tailored quantification techniques
State of the art pharmacokinetic studies in neonates are based on population pharmacokinetics and low volume samples (plasma, dried spot blood). This necessitates the development of tailored quantification techniques. Most of the excipients, including PG, are small molecules that may evaporate. Consequently, the use of dried spot blood techniques should be validated
To what extent can PG pharmacokinetics be extrapolated?
In addition to median estimates on PG clearance in (pre)term neonates, it is to be anticipated that other disease characteristics (renal failure, hepatic failure, peripartal asphyxia) or treatment modalities (formulations containing ethanol, whole body cooling) warrant further study. Similarly, accumulation may result in zero order instead of first order kinetics (De Cock et al., 2012)
What are useful pharmacodynamic outcome variables in neonates?
The current indicators applied to assess renal, hepatic and metabolic tolerance of low dose PG exposure in neonates are based on similar (in)tolerance studies in adults and all relate to accumulation and the subsequent osmolar changes. Differences in permeability of the blood–brain barrier, differences in sensitivity to osmolar shifts or synergistic pharmacodynamic effects (e.g. propylene glycol + phenobarbital, Lau et al., 2012) may result in population specific pharmacodynamics

3. Discussion and conclusions

At present, the data on PG disposition and tolerance suggest that there is a lower limit of PG exposure in neonates. Such lower level of exposure should be based on estimated clearance, but has to take the extensive variability in clearance within neonatal life into account. In addition to PG specific observations, we hereby illustrate the feasibility to document aspects of excipient disposition in neonates. Recently, Whittaker et al. refocused on the issue of exposure to solvents – including PG – in formulations routinely administered to (pre)term neonates and stated that there is a need to determine safety and tolerance of expicients in this specific population (Whittaker et al., 2009).

In addition to PG specific observations, a framework to document excipient disposition was provided. The issues we encountered during the PG project have been summarised in Table 1. Obviously, this approach can be considered to study aspects of pharmacokinetics and -dynamics of other excipients (e.g. ethanol, benzylalcohol, sorbitol) and preservatives (e.g. parabens) in this specific population.

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