Clinical pharmacology of propylene glycol in neonates

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Abstract: Propylene glycol (PG) is an unintentionally frequently co-administered solvent together with a therapeutic compound, despite the fact that PG accumulation potentially results in hyperosmolarity, lactic acidosis and renal/hepatic toxicity. By their nature, newborns are expected to have ‘physiological’ impaired hepatic and renal elimination capacity. Focused studies in neonates should enable us to unveil data on PG clearance and tolerance in this population. In consecutive steps, we documented PG disposition following iv administration of PG and renal PG elimination in neonates, and compared these findings with observations in adults. Finally, we documented aspects of tolerance of PG in neonates. The data on PG disposition and tolerance suggest that there is a lower limit of safe short term exposure to PG in neonates. Such a safer level of exposure should finally be based on clearance estimates and level of tolerated exposure. Besides the compound specific observations, we illustrated that it is feasible and possible to prospectively assess aspects of disposition and tolerance of solvents in neonates.

Key-Words: formulation – propylene glycol – newborn – maturation – developmental toxicology

1 Introduction

History provides us with evidence on the deleterious effects of chloramphenicol (gray baby syndrome), benzyl alcohol (gassing syndrome) or dexamethasone (cerebral palsy) in neonates [1,2]. These anecdotal observations illustrate that ‘children are not just small adults’ neither are ‘newborns just small children’. There are age-dependent changes in body composition: almost all phase I and phase 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 affect pharmacokinetics (concentration-time, PK) [1,2]. Besides or in addition to differences in effects due to differences in pharmacokinetics, there may also be specific differences in pharmacodynamics (PD) due to age-related differences in e.g. receptor expression, receptor activation or post-receptor mechanisms.

Besides the active compounds, formulations used for intravenous administration of drugs frequently necessitates the addition of a solvent in order to ensure aqua solubility and stability of a given drug throughout a given shelf life over a given temperature range or other external conditions. One of the co-solvents frequently applied, is propylene glycol (PG). Propylene glycol (1,2 propanediol) is a clear, colourless, odourless, water-soluble alcohol. Physically, it is similar to ethylene glycol but it is much less toxic although toxic effects have been described [3,4]. PG can cause lactic acidosis, increase in anion gap or osmolar gap, hyponatraemia or hepatic dysfunction (increase direct bilirubinaemia). Other side effects such as haemolysis, mental status changes or renal toxicity (e.g. renal tubular acidosis, acute tubular necrosis resulting in increased creatinaemia and oliguria) have been reported as manifestations of PG accumulation and toxicity [3-9]. Most of the reports in adults relate to continuous intravenous administration of sedatives (i.e. lorazepam, diazepam) with co-administration of PG.

In adults, about 45 % is eliminated by renal route, 55 % undergoes hepatic metabolisation through lactate and pyruvate [10]. Therefore, patients with alterations in hepatic and/or renal elimination capacity are at increased risk for PG accumulation and subsequent metabolic and/or clinical symptoms [10]. By their nature, newborns are expected to have ‘physiological’ impaired hepatic and/or renal elimination capacity [2,11]

It is to be anticipated that due to maturational aspects, PG clearance capacity will differ during childhood. As this will be even more pronounced in (pre)term neonates, observations in paediatric age categories are needed [1,2]. Chicella et al. published a paper on the extent of propylene glycol accumulation associated with continuous infusion of lorazepam in 11 paediatric intensive care patients (age range 1-15 months) and documented accumulation during continuous infusion.
without clinical and laboratory abnormalities [7]. In neonates, there are observations on the intolerance to PG in preterm neonates following exposure up to 3000 mg/day for at least 5 days [8]. These levels of exposure resulted in both biochemical (hyperosmolarity, lactic acidosis, increased creatinaemia, increased direct bilirubinaemia) as well as clinical symptoms (i.e. seizures). The same group estimated PG elimination half life to be 10 to 31 h in neonates compared to 2-5 h in adults, but were unable to explain the in between variability observed [8].

In the current paper, we summarize the consecutive steps made to generate more robust data on PG disposition and tolerance in neonates. For ethical reasons and also to improve both feasibility and clinical relevance of the observations, we collected observations in neonates who were exposed to intravenous drugs formulated with PG (e.g. acetaminophen, phenobarbital, diphantoin, digitalis). These compounds were prescribed because of the individual clinical needs.

2 Problem Formulation

Formulations of drugs for intravenous administration usually contain a solvent to ensure solubility and stability of the drug. One of the co-solvents frequently used is propylene glycol (PG). Propylene glycol (1,2 propanediol) is a clear, colourless, odourless, water-soluble alcohol. Physically, it is similar to ethylene glycol but it is much less toxic although toxic effects usually contain a solvent to ensure solubility and stability of the drug. One of the co-solvents frequently used is propylene glycol (PG). Propylene glycol (1,2 propanediol) is a clear, colourless, odourless, water-soluble alcohol. Physically, it is similar to ethylene glycol but it is much less toxic although toxic effects have been described [3,4]. Median PG clearance in non-critically ill adult patients is 15.9 L.h\(^{-1}\) and was only modestly lower (14.6 L.h\(^{-1}\)) in critically ill adults [10]. About 45 % is eliminated by renal route, and 55 % undergoes hepatic metabolism through lactate and pyruvate. Therefore, patients with alterations in renal and/or hepatic elimination capacity are at increased risk for PG accumulation and subsequent metabolic and/or clinical symptoms.

Toxicity to PG in preterm neonates has been reported following exposure of up to 3000 mg.day\(^{-1}\) for at least five days (parenteral nutrition solutions) [8]. Toxicity was both clinical (seizures) and biochemical (hyperosmolarity, lactic acidosis, raised plasma creatinine and bilirubin). [8] The same group estimated PG elimination half life to be 10 to 31 hours in neonates compared to 2-5 h in adults, but were unable to explain the interindividual variability within their cohort of neonates.

Recently, Whitakker et al. refocused on the issue of exposure to solvents - including PG - in formulations routinely administered to neonates [3]. These authors stated that there is a need to determine safety and tolerance of excipients in this specific population. Unintentional PG co-administration together with active compounds is currently routine practice in neonates. We therefore took the decision to collect data on disposition and (in)tolerance of PG in neonates in a single neonatal intensive care unit and used our experience to perform clinical pharmacological studies in this specific population [2, 12, 13].

Focused studies in neonates should enable us to unveil data on PG tolerance and clearance and in covariates in this population. In consecutive steps, we documented PG disposition following iv administration of PG in neonates (3.1), we documented renal PG elimination and compared these findings with earlier reported observations in adults (3.2). Finally, we documented aspects of tolerance of PG in neonates (3.3). For the PD disposition study (3.1, 3.2), we focus in this paper only on observations collected following iv acetaminophen exposure (Paracetamol synthetica\(^{®}\), 800 mg PG/1000 mg acetaminophen). For aspects on PG tolerance (3.3), several formulations (cf supra) were considered.

The dosing regimen of iv acetaminophen was based on a loading dose (20 mg.kg\(^{-1}\), equal to 16 mg.kg\(^{-1}\) PG), followed by a postmenstrual age dependent maintenance dose (5-10 mg.kg\(^{-1}\) q6h, equal to 4-8 mg.kg\(^{-1}\) PG [14, 15]). We aimed to collect urine samples following first exposure only (collection urine in the first 6 h after iv administration) and 24 h urine collections during repeated administration. Time-concentrations plasma profiles were collected when an arterial line was available.

The study was conducted in Leuven Neonatal Intensive Care Unit (NICU) following approval by the ethical committee of the University Hospitals Leuven and was registered (www.clinicaltrials.gov, PARANEO study). Neonates were included after informed written parental consent.

3 Problem Solution

3.1. PG disposition in plasma

Patients to whom PG containing formulations like Phenobarbital (Lumina\(^{®}\)), diphantoin (diphantoine\(^{®}\)) or iv acetaminophen (paracetamol synthetica\(^{®}\)) were administered and in whom blood sampling through arterial access was available, were considered.

Time, duration, PG dose and time of sampling were recorded. In figure 1, the PG time-concentration profiles...
following iv acetaminophen loading dose (20 mg/kg, equal to 16 mg/kg PG) are provided.

Assuming a one-compartment model and following 16 mg.kg\(^{-1}\) PG exposure, peak concentration are around 40 mg.l\(^{-1}\), suggesting a distribution volume of 0.5 l.kg\(^{-1}\) while the elimination half life is (visually) estimated to be 6-12 h. Most PG concentrations remain below 50 mg.l\(^{-1}\).

Continued collections of blood/plasma samples and the link between time-concentration profiles and clinical characteristics through population pharmacokinetic modelling should enable us to further estimate clearance and its covariates. Based on such estimates, we can at least predict at which level of PG threshold as suggested in adults will be reached.

3.2. PG renal elimination characteristics

As mentioned earlier, patients with alterations in hepatic and/or renal elimination capacity are at increased risk for PG accumulation and subsequent metabolic and/or clinical symptoms [5,10].

As an additional, non-invasive step, we aimed to quantify primary contribution of PG renal elimination to overall PG renal elimination following single and repeated dose PG exposure. This approach was in part based on our earlier experience to use urine collections to unveil aspects of drug disposition in neonates [2].

Neonates treated with intravenous paracetamol Sintetica© (Sintetica, Mendrisio, Italy, 800 mg PG/1000 mg paracetamol) and with a bladder catheter were considered for recruitment. Clinical characteristics (weight, postnatal age, gestational age, postmenstrual age, diuresis) were prospectively collected. Before inclusion, nursing files were screened for other sources of either intravenous or oral PG.

Urine collections following the initial loading dose (16 mg/kg PG) exposure were available in 25 neonates [14,15]. Median relative contribution of renal PG elimination to the total PG exposure in this cohort of neonates was 7% and increased to 19% when the urine collection was extended (18/25) to 24 h and following median exposure of 40 mg/kg PG. This is significantly lower than the 45 % eliminated by renal route as mother compound in adults [10]. This suggests that the contribution of renal compared to metabolic route for PG elimination differs between neonates and adults and reflects renal elimination immaturity in early life [11].

Infants display maturation in the disposition of exogenous compounds and these maturational changes are even more pronounced in neonates [1,2]. There are age-dependent changes in body composition and almost all phase I and phase II metabolic processes mature. In addition, renal drug clearance in early life is low and almost completely depends on glomerular filtration rate (GFR). Age-specific PG clearance capacity will therefore depend both on ontogeny of metabolic clearance (alcohol dehydrogenase) as well as on the primary renal elimination (GFR) of the parent compound. However, these processes (hepatic versus renal) do not mature simultaneously as was recently illustrated for tramadol disposition in infancy [16].

Alcohol dehydrogenase (ADH) ontogeny has been reviewed by Hines et al.[17] Although ADH maturation is to a certain extent iso-enzyme specific – with faster maturation of ADH1 compared to ADH2/ADH3 - the proteins and enzyme activities of these iso-enzymes are present in the 3th trimester of pregnancy and in neonates. Based on in vitro observations, it is to be anticipated that there is already relevant metabolic clearance capacity for PG in neonates. In contrast, maturation of GFR and tubular secretion/resorption is delayed in early neonatal life, resulting in overall low clearance and extensive inter-subject clearance variability for drugs exclusively eliminated by renal route (e.g. aminoglycosides, glycopeptides) [11,18,19].
3.3. Assessment of PG tolerance in neonates [20]

Besides aspects of disposition, data on (in)tolerance were collected. Biochemical indicators of PG related toxicity were based on earlier mentioned biochemical indicators as reported in literature and relate to renal [creatininaemia, plasma sodium, diuresis] or metabolic [Base Excess (BE), Anion Gap (AG), lactate, bicarbonate] disturbances.[3-9] To facilitate sampling, and to make observations throughout time comparable, only patients with an arterial line were included. All observations available from 48 h before up to 48 h after the last PG exposure were collected. In cases treated with iv acetaminophen, indicators of hepatic [aspartate aminotransferase (AST), alanine transaminase (ALT), direct bilirubinaemia] dysfunction and clinical characteristics were compared with observations as described earlier in literature in a historical dataset collected in the same NICU, using the same dosing regimen, but following the administration of another, not PG, but mannitol containing intravenous paracetamol (Perfalgan, Bristol Myers Squibb, Braine l’Alleud, Belgium) formulation.[21]

Based on 5 566 observations prospectively collected in 69 neonates before, during or following a median PG exposure of 34 (range 14-252) mg/kg/24h, progressive postnatal adaptation in renal, metabolic and hepatic function were documented, unrelated to the PG exposure [20]. Plasma creatinine decreased significantly during PG exposure. This is however not unexpected in neonates who have impaired renal function as part of their normal physiology at birth. Similarly, diuresis increased significantly in the first 24 hour period. For the indicators of metabolic balance, similar trends were documented with significant changes towards normalisation [22]. Hepatic indicators remained stable throughout the time interval of the study. In the subgroup of 40 cases treated with iv PG-paracetamol, observations on renal and hepatic function were similar to a historical cohort of published observations following exposure to iv mannitol-paracetamol [21].

In a post hoc analysis, paired observations were analysed dichotomous in cases with either or not a PG exposure of > 40 mg/kg/24h in search for a potential exposure-effect there were no significant differences in tolerance between both levels of PG exposure.

Although preliminary conclusions are only based on biomarkers initially reported in adults and only focus on short term outcome, the current observations on PG tolerance suggest that there is a lower limit of safe short term exposure to PG in neonates similar to the spectrum concept of adult safe exposure level.

3.4 General discussion

The need to evaluate the safety of excipients in neonates has recently been highlighted [3,9]. PG is a frequently applied solvent for drugs administered intravenously to neonates [5-9]. Consequently, we tried to unveil aspects of PG disposition and tolerance in neonates.

Firstly, based on the first time-concentration profiles, we can roughly estimate the distribution volume to be about 0.5-0.6 l/kg, while elimination half life (raw estimate) is 6-12 h. Compared to observations in adults, the distribution volume seems relatively similar, while elimination half life in neonates (6-12 h) is significantly longer compared to adults (2.3 h), reflecting reduced (metabolic and/or renal) clearance [1,2,10].

Secondly, in an attempt to further unveil aspects of PG elimination routes (either metabolic or primary renal), data on renal PG elimination were collected. Until more extensive datasets have been collected, it seems that renal elimination of PG is only a modest contributor (10-20%) to overall elimination in neonates compared to adults (50%). The present observations on the differences in relative contribution of renal PG elimination in neonates compared to adults therefore re-emphasizes the overall impact of ontogeny of renal elimination processes.

Further collection of observations in both plasma and urine should enable us to quantify exactly the contribution of both hepatic metabolic clearance and renal elimination clearance to overall clearance. We at least confirm the overall decreased clearance (figure 1-2) within this population. This is in line with other in vivo observations on hepatic or renal eliminated drugs, and seems to be essential in neonatal pharmacology: in addition to the overall low median clearance, there is extensive in between variability [11,12,18,19,23].

Finally, based on prospective collection of indicators of renal, metabolic and hepatic function in 69 neonates, we were unable to detect any short term biochemical impact during or following a median PG exposure of 34 (14-252) mg/kg/24h [20].

Although the active comparator approach (different acetaminophen formulations) is a strong argument in support of the tolerance to a median PG exposure of 34 mg/kg/24h in neonates, we hereby do not have the intention to suggest PG is harmless. As mentioned earlier, there are reports on PG related side effects in neonates, however following much higher levels of PG exposure.[3-9] In addition, this study only focuses on short term tolerance using a limited number of biomarkers, initially validated for use in adults.
4 Conclusion

Conclusions should be formulated cautiously since still the number of observations is limited. However, the data on PG disposition and tolerance suggest that there is a lower limit of safe short term exposure to PG in neonates similar to the spectrum concept of adult safe exposure level [2,6]. Ultimately, such a safer level of exposure should be based on clearance estimates, the level of tolerated exposure (below a given PG concentration) and needs further validation. Besides the compound specific observations, we illustrate that it is feasible and possible to prospectively assess aspects of disposition and tolerance of solvents in neonates. We were able to collect PG data in an in vivo neonatal setting by collected biochemical data and collecting PG concentration-time profiles in neonates to whom this compound is unintentionally co-administered. We are confident that these findings and the approach used are of high clinical relevance to both neonatologists and clinical pharmacologists and that other biomarkers should be studied and validated in the neonatal period [15,16].

References: