1st ESNEE EXCIPIENT MONOGRAPH: INFORMATION NEEDED TO FORMULATE, PREPARE AND PRESCRIBE MEDECINES FOR NEONATES CONTAINING PROPYLENE GLYCOL AS AN EXCIPIENT

BACKGROUND:

Neonates are particularly vulnerable to adverse effects of medicines and excipients because of organ immaturity. ESNEE (European Study of Neonatal Exposure to Excipient) is a European research consortium granted in 2011 by ERA-NET PRIOMED-CHILD.

AIMS:

Establish a monograph to inform on Propylene glycol use in neonate.

CONCLUSION:

This is the first monograph of propylene glycol offering a complete over view validated by a panel of European experts. This document should help the Pharmaceutical industry and hospital pharmacists when formulating/preparing medicines and neonatologists when prescribing such PG containing medicines. It also provides a clear image of which information is lacking and warrants further experimental investigation.

MATERIALS&METHODS:

Organisation:

ESNEE CONSORTIUM : 5 Partner (Project Leader: Dr. Mark Turner, Senior Lecturer in Neonatal Medicine and Neonatal Consultant)

Lack of information
For practitionners and pharm Industry
-To prescribe
-To formulate

Extract most relevant papers

Analyse/summarize relevant Data

Re-phrase Data

Useful/practical information for practitioners and Pharm Industry

Method :

Identify and access to database

- *bibliographique databases:* Medline, Web of Science, Pascal, International Pharmaceutical Abstracts, Biosis previews, Embase
- *Factual databases:* Toxnet, chemIdPlus, RepTox
- *Books*

Record and organize Data

- 1500 hits → 87 hits relevant for ESNEE
- Tox. Profil writting

Consult experts

- Clinicians
- Pharmacologists
- pharmacists
- Toxicologists

RESULTS:

DIFFERENT KINDS OF DATA:

- GENERAL INFORMATION
- TOXICOKINETICS
- TOXICITY
- MONITORING
- ESNEE POINT OF VIEW

LEVEL OF INFORMATION:

- Neonate data
- Extrapolation from adult data
- No human data

RISK LEVEL IN NEONATE:

- LOW RISK — SAFE USE
- RELATIVE RISK — To be use with caution
- HIGH RISK — «To be banned »

ESNEE POINT OF VIEW

BE AWARE OF MULTIPLE EXPOSURE
- Widely used in oral solution and topics.
- ***Don't forget cosmetics***

BE AWARE OF TOXICITY
- Acute Adverse effects were observed for newborn

BE AWARE OF TOXICOKINETIC
- Delayed elimination compared to adults

BE AWARE OF FIRST SIGNS OF INTOXICATION
- osmolar gap follow Up

Take PG exposure into account

GENERAL INFORMATION

- Molecular formula: C3H8O2
- Molecular Weight: 76.09442 g/mol
- CAS NUMBER: 57-55-6
- Synonyms: 1,2-propanediol, propane-1,2-diol, 1,2-propylene glycol, Trimethyl glycol, Methylethylglycol, 2-hydroxypropanol, 2,3-propanediol, E1520

- Use:
  industry of food, pharmaceutics, chemist
  Conservateur, humectant, plastifiant, solvant, agent stabilisateur, cosolvant

- Regulation:

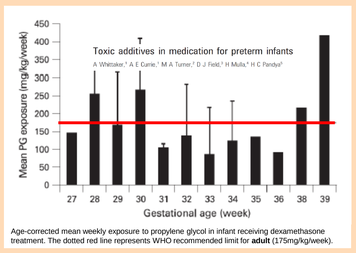
WHO: Acceptable daily intake **0-25mg/kg/day**

FDA: PG is currently listed as Generally As Safe)
EMA**: 200mg/kg/day** may cause alcohol-like symptoms for children.

Example of uses of propylene glycol in pharmaceutical industri:

Use	Dosage Form	Concentration (%)
Humectant	Topicals	≈ 15
Preservative	Solution, semisolids	15-30
Solvent or cosolvent	Aerosol solution	10-30
	Oral solutions	10-25
	Parenterals	10-60
	Topicals	5-80

Example of neonatal exposure



Age-corrected mean weekly exposure to propylene glycol in infant receiving dexamethasone treatment. The dotted red line represents WHO recommended limit for **adult** (175mg/kg/week).

Some infants being exposed to concentrations in excess of recommended guidelines for maximum exposure in adults.

References:

1. FDA. Generally recognized as safe. 1982; 21 CFR 184.1666

2. WHO. Toxicological evaluation of some food additives including anticaking agents, anti-microbials, antioxidants, emulsifiers and thickening agens. Geneva: World Health Organization; 1974.

3. American Academy of Pediatrics, Committee on Drugs. "Inactive" ingredients in pharmaceutical products: update (subject review). Pediatrics. 1997;99:268-78.

4. Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC. Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F236-40.

5.http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412. df (last access: March 2013)

6. http://ichem.sis.nlm.nih.gov/chemidplus/ ProxyServlet?objectHandle=DBMain&actionHandle=default&nextPage=jsp/chemidheavy/ResultScreen.jsp&TXT(last access: March 2013)

- **No regulation for children or newborn**
- **Multiple sources of exposure**
- **Relative exposure higher in newborn**

TOXICOKINETIC

Absorption:

- *Oral:* Cmax : 1h Bioavailability might be 100%
- *Dermal:* PG is absorbed through irritated/burned skins.
  PG is absorbed by neonate skin.
- *Inhalation*: 5% of dose are found in the blood.

	ADULTE	**NEONATE**
Volume of distribution	0.52 L/kg orale, 0.77– 0.79 L/kg rectale, 0.55– 0.94 L/kg IV. 11	**0.18 L/kg (IV)**
elimination	Kidney:45% unchanged. Liver: 55% → lactacte & pyrurate	**Kidney: 7% unchanged** **Liver: unclear but different from adult (ALDH ontogenesis)**
clearance:	8.64 - 23.4L/h/1.73m² (means 15,9L/h/1.73m²)	**0.0849 L/h**
Half-life	2.4 à 5.2 hr	**10.8 à 30.5h** **8.88h. (6 to 12h)**

Delayed elimination → Accumulation ?

References:

1. Yu, D. K., Elmquist, W. F. and Sawchuk, R. J. Pharmacokinetics of propylene glycol in humans during multiple dosing regimens. J Pharm Sci 1985; 74: 876-9

2. Speth, P. A., Vree, T. B., Neilen, N. F., de Mulder, P. H., Newell, D. R., Gore, M. E. and de Pauw, B. E. Propylene glycol pharmacokinetics and effects after intravenous infusion in humans. Ther Drug Monit 1987; 9: 255-8

3. Rolloffel, W. J., Weekers, L. E. and Goldhoorn, P. B. Pharmacokinetics of propylene glycol after rectal administration. Pharm World Sci 1996; 18: 109-13.

4. Ruddick, J. A. Toxicology, metabolism, and biochemistry of 1,2-propanediol. Toxicol Appl Pharmacol 1972; 21: 102-11.

5. Yu, D. K. and Sawchuk, R. J. Pharmacokinetics of propylene glycol in the rabbit. J Pharmacokinet Biopharm 1987; 15: 453-71

6. Allegaert K, Vanhaesebrouck S, Kulo A, Cosaert K, Verbesselt R, Debeer A, de Hoon J. Prospective assessment of short-term propylene glycol tolerance in neonates. Arch Dis Child.2010;95:1054-1058

7. De Cock RF, Knibbe CA, Kulo A, de Hoon J, Verbesselt R, Danhof M, Allegaert K. Developmental pharmacokinetics of propylene glycol in preterm and term neonates. Br J Clin Pharmacol. 2012 April

8. Kulo A, Allegaert K, de Hoon J, Verbesselt R. Determination of propylene glycol in low volume plasma and urine samples of neonates by LC with photodiode array detection. Chromatographia. 2011;73:463–470. doi: 10.1007/s10337-011-1923-8.

9. MacDonald MG, Getson PR, Glasgow AM, Miller MK, Boeckx RL, Johnson EL. Propylene glycol: increased incidence of seizures in low birth weight infants. Pediatrics. 1987;79:622–625.

10. Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP, Goodman SI. Hyperosmolality in small infants due to propylene glycol. Pediatrics. 1983;72:353–355.

TOXICITY

Chronic:

ANIMAL DATA

Intermediate and chronic exposure to PG may lead to changes in hematological parameters and hemolysis of red blood cells. (Cats, dog)

Acute:

Some case reports among Adults, infants & newborns.

NEONATE HUMAN DATA

Assess tolerence of PG exposure to neonates:
Median **34mg/kg.day (range 14-252)** PG exposure does not affect postnatal renal, hepatic and metabolic adaptation

- **Central Nervous System**
  - **Depression**
  - **Seizure**
  - **Coma**
- **Kidney:**
  - **Renal failure**
  - **Blood in urea**
- **Liver:**
  - **hepatic lesion**
- **Metabolic:**
  - **Acidosis**
  - **Hyperosmolality**
  - **Increase omolar Gap**

NEONATE HUMAN DATA

☞Lack of data

?

☞Long term neurological effect?

NEONATE ANIMAL DATA

Propylene glycol produces excessive apoptosis in the developing mouse brain, alone and in combination with phenobarbital

References:

1. National Toxicology ProgramN. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol (PG). NTP CERHR MON. 2004 Mar;(12):i-III6.

2.. ATSDR. Toxicological profile for ethylene glycol and propylene glycol. Atlanta (GA): Agency for Toxic Substances and Disease Registry; 1997.

3.Werley, M. S., McDonald, P., Lilly, P., Kirkpatrick, D., Walkery, J., Byron, P., & Venitz, J. (2011). Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs [relevant]. Toxicology (Amsterdam), 287(1-3), 76-90.

4.Lau, K., Swiney, B. S., Reeves, N., Noguchi, K. K., & Farber, N. B. (2012). Propylene glycol produces excessive apoptosis in the developing mouse brain, alone and in combination with phenobarbital. Pediatr Res, 71(1), 54-62.

5.Thackaberry, E. A., Kopytek, S., Sherratt, P., Troutz, K., & McIntyre, B. (2010). Comprehensive investigation of hydroxypropyl methylcellulose, propylene glycol, polysorbate 80, and hydroxypropyl-beta-cyclodextrin for use in general toxicology studies. Toxicol Sci, 117(2), 485-492

6.Enright, B. P., McIntyre, B. S., Thackaberry, E. A., Treinen, K. A., & Kopytek, S. J. (2010). Assessment of hydroxypropyl methylcellulose, propylene glycol, polysorbate 80, and hydroxypropyl-beta-cyclodextrin for use in developmental and reproductive toxicology studies. Birth Defects Res B Dev Reprod Toxicol, 89(6), 504-516

7.Guillot, M., Bocquet, G., Eckart, P., Amiour, M., el-Hachem, C., Garnier, R., Hagenoer, J. M. (2002). [Home environment and acute propylene glycol intoxication in a two-year old. An unusual case report]. Arch Pediatr, 9(4), 382-384.

8. Peleg, O., Bar-On, B., & Arad, I. (1998). Coma in a premature infant associated with the transdermal absorption of propylene glycol. [relevant]. Acta paediatrica (Oslo), 87(11), 1195-1196.

9. Glasgow, A. M., Boeckx, R. L., Miller, M. K., Macdonald, M. G., August, G. P., & Goodman, S. I. (1983). Hyperosmolality in small infants due to propylene glycol Pediatrics (Evanston), 72(3), 353-355.

10. I Huggon, I. J., D Macrae. (1990). Hyperpsmolality related to propylene glycol in an infant treated with enoximone infusion (Vol. 301, pp. 19-20): BMJ.

11. Cady, E. B., Lorek, A., Penrice, J., Reynolds, E. O. R., Iles, R. A., Burns, S. P., Cowan, F. M. (1994). Detection of propan-1,2-diol in neonatal brain by in vivo proton magnetic resonance spectroscopy. Magnetic Resonance in Medicine, 32(6), 764-767.

12. Kelner, M. J., & Bailey, D. N. (1985). Propylene glycol as a cause of lactic acidosis [relevant]. Journal of analytical toxicology, 9(1), 40-42.

13. Allegaert, K., Vanhaesebrouck, S., Kulo, A., Cosaert, K., Verbesselt, R., Debeer, A., & de Hoon, J. (2010). Prospective assessment of short-term propylene glycol tolerance in neonates. Arch Dis Child, 95(12), 1054-1058.

14. Chicella, M., Jansen, P., Parthiban, A., Morlowe, K. F., Brenzuh, F. A., Krueger, K. P., & Boerth, R. (2002). Propylene glycol accumulation associated with continuous infusion of lorazepam in pediatric intensive care patients. Crit Care Med, 30(12), 2752-2756

15. MacDonald, M. G., Fletcher, A. B., Johnson, E. L., Boeckx, R. L., Getson, P. R., & Miller, M. K. (1987). The potential toxicity to neonates of multivitamin preparations used in parenteral nutrition. JPEN J Parenter Enteral Nutr, 11(2), 169-171.

16. Macdonald, M. G., Getson, P. R., Glasgow, A. M., Miller, M. K., Boeckx, R. L., & Johnson, E. L. (1987). Propylene glycol: increased incidence of seizures in low birth weight infants Pediatrics (Evanston), 79(4), 622-625

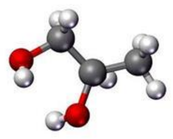
17. Shehab N, Lewis CL, Streetman DD,Donn SM (2009) Exposure to the pharmaceutical excipients benzyl alcohol and propylene glycol among critically ill neonates. Pediatr Crit Care Med;10(2):256-9.

18. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B. Kaletra Oral Solution Toxicity in Neonates - Lopinavir, Ethanol, and/or Propylene Glycol? 18th Conference on Retroviruses and Opportunistic Infections, 2011.

ERA-NET PRIOMEDCHILD

European Study of Neonatal Excipient Exposure

ESNEE Monograph on Neonate exposure of Propylene glycol



MARCH 2013 — *ESNEE publication No. 0001*

Monitoring

Recognition:
- Use osmolar gap at 48h
- Hyperosmolality
- Lactic acidosis
- Clinical effect

Treatment:
- Stop source of PG (recovert within 48h)
- Hemodialysis (rapdly lower PG levels)

Level of PG concentration:
- Serum PG levels have been shown to be proportionate to serum osmolality.
- The estimated osmolar effect of PG can be determined by dividing the PG level by 7,6.
- Formula for predicting serum PG concentration from the osmolal gap (-82.1+[osmolal gap x 6.5]).

☞ Osmolar gap increase => first indicator of PG accumulation before PG toxicity appears.
☞ **A level of PG tolerance has been suggested *only in adult :***
>25 mg/dl = accumulation
>58-60 mg/dl = metabolic abnormalities
>104 mg/dl = clinical symptoms
☞ Acute toxicity is reversible

References:

1.WilsonKC, Reardon C, Theodore AC, FarberHW: Propylene glycol toxicity: a severe iatrogenic illness in ICU patients receiving IV benzodiazepines. A case series and prospective, observational pilot study. Chest 128:1674– 1681, 2005

2. Arroliga AC, Shehab N, McCarthy K, Gonzales JP: Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. Crit Care Med 32:1709–1714, 2004

3. Barnes BJ, Gersz C, Smith JR, Terrell AR, Mullins ME: Osmolal gap as a surrogate marker for serum propylene glycol concentrations in patients receivingLZ for sedation. Pharmacotherapy 26:23–33, 2006

4.Yahwak JA, Riker RR, Fraser GL, Sobak-Sharpe S:Determination of a lorazepam dose threshold for using the osmol gap to monitor for propylene glycol toxicity. Pharmacotherapy 2008; 28: 84–91

5. ParkerMG, FraserGL,WatsonDM,RikerRR: Removal of propylene glycol and correction of increased osmolar gap by hemodialysis in a patient on high dose lorazepaminfusion therapy. IntensiveCareMed28:81–84, 2002

6. Zar T, Graeber C, Perazella MA: Recognition, treatment, and prevention of propylene glycol toxicity. Semin Dial. 2007 May-Jun;20(3):217-9.

7. National Toxicology ProgramN. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol (PG). NTP CERHR MON. 2004 Mar;(12):i-III6.

8. ATSDR. Toxicological profile for ethylene glycol and propylene glycol. Atlanta (GA): Agency for Toxic Substances and Disease Registry; 1997.

9. LaKind, J. S., McKenna, E. A., Hubner, R. P. and Tardiff, R. G. A review of the comparative mammalian toxicity of ethylene glycol and propylene glycol. Crit Rev Toxicol 1999; 29: 331-65.

10. Giacoia GP, Miranda R, West KJ. Measured vs calculated plasma osmolality in infants with very low birth weights. Am J Dis Child 1992; 146: 712-7

P. Vaconsin[1], T. Storme[1], S. Salunke[2], D Masset[3], A. Nunn[4], H. Varendi[5], **J. Carleer[6], M. Turner[4], A. Rieutord[7].**
AP-HP, Hôpital Robert Debré, Pharmacie[1], Paris. FRANCE[1], European Paediatric Formulation Initiative (EuPFi) [2], ANSM, Saint-Denis, France[3], Department of Women's and Children's Health, University of Liverpool, UK[4], University of Tartu, Tartu, Estonia[5], Belgian Federal Agency for Medicines and Health Products, Brussels, Belgium[6] , AP-HP, HUPS, Hôpital Antoine Béclère, Pharmacie, Clamart (France)[7]