Propylene glycol as a pharmaceutical excipient in pediatrics

- Disha Patel

The Utilization of Propylene Glycol as a Pharmaceutical Excipient in the Pediatric Field

Abstract

As a widely used excipient in pediatric formulations, propylene glycol functions as a solvent, emulsifier, humectant, and hygroscopic agent. It is a clear, colorless liquid whose properties enable it to have pharmacodynamic applications. Oftentimes, propylene glycol is combined with other mediations to enhance its penetration. For instance, a combination of 20% propylene glycol and 5% lactic acid in a semiocculusive cream base is used as a highly effective and well-tolerated keratolytic in patients with lamellar ichthyosis and possibly could be in various other hyperkeratotic diseases. Unfortunately, though to a lesser degree, this excipient is associated with toxic effects such as hyperosmolality, hemolysis, and lactic acidosis. Also, in concentrations greater than 10%, propylene glycol may act as an irritant in some patients (“ Health Effects” 2). From a pharmacokinetic viewpoint, there is a potential of renal toxicity associated with propylene glycol and lorazepam. The high concentration of propylene glycol contained in certain intravenous drug products, such as phenytoin, diazepam, digoxin, and etomidate, may induce thrombophlebitis. Here, the patients’ increased serum creatinine concentrations are likely to have resulted from exposure to propylene glycol due to lorazepam infusion. Serum osmolality and osmol gap may be useful markers for propylene glycol toxicity. Much like the above mentioned applications, through its chemical composition, propylene glycol

has the ability to exert a beneficial effect on pediatric formulations (Webbook 5).

Introduction

Propylene glycol, which is also known Propane-1, 2-diol, is a colorless, viscous, organic liquid with a slightly sweet taste. This excipient is utilized in food, cosmetics and pharmaceutical preparations. Examples of pharmaceutical applications include therapeutic drugs such as vaccines, cough syrups, local anesthetics, antiseptics, vitamins, and hormones. It is produced through the fermentation of yeast and carbohydrates. Propylene glycol is industrially made from propylene oxide. It is made from either a catalytic or a non-catalytic method which exposes the propylene into extremes of temperature and a small amount of sulfuric acid or alkali to yield propylene glycol for industrial purposes (“ Frequently Asked Questions about Propylene Glycol” 1).

It is concluded that, with extensive research, this excipient is categorized as safe in the body. According to the Agency for Toxic Substances & Disease Registry, in the body, under conditions of normal low exposure, propylene glycol is quickly metabolized and excreted. Its metabolic pathway is comparable to that of sugar: propylene glycol is quickly converted into lactic acid, similar to what happens with the energy in the muscles when exercising. Afterwards, the lactic acid is excreted via urine (“ Database of Select Committee on GRAS Substances (SCOGS) Reviews” 2). Surprisingly, from a toxicological point of view, alcohol is more toxic than propylene glycol. Propylene glycol has been used safely for more than 50 years in a

large variety of applications. As a result, it is effectively used in prescription medications such amoxicillin (500 mg), clindamycin hydrochloride (150 mg & 300 mg), gabapentin (300 mg), lyrica (50 g & 75 mg), and omeprazole (20 mg) (“ Result Filters” 4).

Through statistical data, it is overwhelmingly evident that there is a continually growing market for propylene glycol. According to the IHS website, United States (19%), Western Europe (39%), Japan (17%), and China (80%) had the largest consumption (“ Inactive Ingredients in Pharmaceutical Products” 5). Since it has been proven safe with a relative low toxicity level, it is projected that the consumption of propylene glycol will rise (*IHS Home Page* 4).

The Effects of Propylene Glycol in Pediatrics

Pharmaceutical medications are composed of two very essential ingredients: active pharmaceutical ingredients (APIs) and excipients. The purpose of the active pharmaceutical ingredient in a drug is to elicit a specific therapeutic effect on the patient. Specifically, when the drug is consumed, it will exert a necessary effect on the body in order to produce an ideal outcome: the therapeutic response (“ TOXICOLOGICAL PROFILE FOR PROPYLENE GLYCOL 3”). The component of the drug is the excipient, which is an inactive ingredient utilized for possible multifunctional usage. For instance, an excipient can be binders, coatings, diluents, disintegrants, fillers, flavors, colors, lubricants, glidants, sorbents, preservatives, sweeteners, and solubilizing agents. Oftentimes, they do acquire some extent of therapeutic acclivity, though less than the API. Similar to many other drugs, propylene

glycol functions both, as an API and excipient-an indication that multiple functions can have multiple benefits (*AccessMedicine* [41168448] 2).

Additionally, medications are tailored to a specific age group to maximize the therapeutic effect for the patient. Therefore, criteria for an ideal drug for the pediatric population will undoubtedly differ from the criteria for the geriatric population. Routes of administration suitable for pediatrics include oral, topical, rectal, inhalation, injectable and drop (eye, ear, and nose). Propylene glycol enters the body as an alcohol and metabolizes in the body's enzyme pathways. These pathways do not mature in humans until 12 to 30 months of age. Proper judgment when administering a propylene glycol-based formulation to neonates is crucial in order to prevent potential complications (PubChem 1).

In comparison to adults, new born babies have a propylene glycol half-life of 16. 9 hours rather than a significantly lower 5 hour half-life for adults. In one study, the use a multivitamins whose contents included propylene glycol resulted in serum osmolality in low-birth-weight premature babies. However, in another research activity, phenobarbital injections containing propylene glycol were deemed to have an inconsequential effect on the osmolar gap (*AccessMedicine* [40400741] 4). A higher amount of propylene glycol delivered per dose, such as 3 grams, is known to cause more seizures in infants, in comparison to those receiving lesser amounts per dose, such as 300 mg. In a population of 262 patients treated for burns, roughly 3 percent were the result of topical propylene glycol which resulted in hyperosmolality (" Potential Safety Concerns with the Large Amount of Propylene Glycol" 2).

Since propylene glycol is a liquid excipient, it affects the gastrointestinal tract. However, studies of people and animals show that if you have repeated eye, skin, nasal, or oral exposures to propylene glycol for a short time, you may develop some irritation. Furthermore, extensive studies performed have concluded that there are no severe risks of propylene glycol in infants. Thus, it is assumed to be safe if consumed in moderation. The oral liquid formulation also illustrates a high compliance rate amongst infants. Simple considerations such as route of administration and effective concentrations can help achieve a therapeutic response (*AccessMedicine* [40400741] 6).

The chemical composition of propylene glycol is relatively simple: alcohol groups with a hydrocarbon backbone. To an extent, this simplistic structure plays a broad role in various applications ranging from industrial to pharmaceutical uses. Generally, neonates can be exposed to propylene glycol orally or topically. Absorption through oral intake is significantly more effective than on the skin. Once propylene glycol reaches the site of action, it is rapidly metabolized and subsequently excreted (“ A-Z Index” 9). In the blood stream, the half-life of the excipient is approximately 2-4 hours in adults. However, in neonates, it is drastically longer (17 hours). Pertaining to its mechanism of action, it is further metabolized to lactate which is further metabolized to pyruvate, carbon dioxide, and water. Through utilization of the gluconeogenic pathway, glucose is formed. Even though the safety the propylene is apparent, extremely large exposures to propylene glycol have the potential to result in lactic acidosis and hyperosmotic changes in the blood (“ Health Effects” 4).

Extensive research has provided sufficient evidence on the safety and quality of this excipient. To begin, numerous sources indicate that propylene glycol has a dramatically low degree of toxicity. It is associated with moderately low concern for acute toxicity by ingestion, skin contact, and inhalation. There have been reports of altered nervous system function because of high oral exposure to propylene. Normal metabolism of this excipient can be negatively affected through blood pH and osmotic changes. Furthermore, animal studies also confirm the relative low risk of propylene glycol (Webbook 2). For example, a longitudinal study performed on rodents with extremely high exposures to the excipient presented no indication of adverse effects. Consequently, a similar study performed on cats illustrated hematological changes. High aerosol concentrations inhaled by rats caused minor nasal and ocular signs that may have been due to mild irritation or drying effects of propylene glycol on mucous membranes. On a positive note, there is no correlation to cancer from the use of propylene glycol (*AccessMedicine* [45774923] 1).

Pharmacological Profile of Propylene Glycol

Propylene glycol, with a formula $C_3H_8O_2$, is readily miscible with water, acetone, and chloroform. In reference to its structure, it contains an asymmetrical carbon atom, so it has two enantiomers. Since the commercial product is a racemic mixture, pure optical enantiomers can be achieved by the hydration of optically pure propylene oxide. Upon the mixture of propylene glycol and water, the freezing point of water is drastically depressed. Because of this, it is used as a de-icing fluid for vehicles. With the exception of ethylene glycol, glycols are generally known to be non-corrosive

and have low volatility and toxicity. Even with the strict criteria established for pediatrics, propylene glycol satisfies the requirements for safe administration to pediatric patients (“ A-Z Index” 5).

Furthermore, it is derived from propylene oxide and its production methods include either catalytic- proceeds at 150 °C to 180 °C in the presence of ion exchange resin or a small amount of sulfuric acid or alkali, or non-catalytic-high-temperature process at 200 °C to 220 °C (IHS Home Page 3).

Even though this paper focuses mainly on propylene glycol’s purpose as an excipient in pediatric formulations, it has an overwhelmingly degree of other applications. A certain amount (45%) is used as chemical feedback for the manufacture of unsaturated polyester resins. Chemically speaking, propylene glycol reacts with a mixture of unsaturated maleic anhydride and isophthalic acid to give a copolymer. Continuing further crosslinking, thermoset plastics are produced from the unsaturated polymers. Similarly, propylene glycol also reacts with propylene oxide to produce oligomers as well as polymers that are utilized to form polyurethanes (“ Frequently Asked Questions about Propylene Glycol” 2).

As proven be multiple research articles, this excipient is proven safe. The extent of safety is measured by plasma concentration: “ Serious toxicity generally occurs only at plasma concentrations over 1 g/L, which requires extremely high intake over a relatively short period of time.” However, there is always an uncertainty and accidental occurrences. For instance, rare cases of propylene glycol poison were largely related to either inappropriate

intravenous administration or accidental ingestion of enormously large quantities by children (“ Hazardous Substance Fact Sheet” 9).

Conclusion

As proven through this research paper, propylene glycol is an effective ingredient for pediatric use. Since there was no established linkage between cancer and its use, it is popular for multiple uses. Several considerations should be utilized in formulating pediatric medications-specifically, the ingredients in the formulation. With its multiple uses, propylene glycol is well-suited for children for its safety and effectiveness. Like all ingredients, propylene glycol may produce adverse effects in the patient, but drastically less harmful than others. Since an enormous quantity must be consumed before toxicity level is reached, it is well suited for children. With viscous properties, upon consumption, it has the potential to elicit a faster therapeutic effect on the patient. Therefore, it is both potent and efficacious. In all, this ingredient proves to be a significant element to the overall formulation of a medication, regardless of the age group targeted (Webbook 5).

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