

Promethazine Syrup Banned: Alteration of Glycerine by the Diethylene Glycol and Ethylene Glycol

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Abstract— The World Health Organization (WHO) intervened after an increase in acute kidney injury cases among children under five in late July 2022, due to the toxic chemical contamination of Promethazine syrup, which contains diethylene glycol and ethylene glycol, leading to 66 deaths in The Gambia. Diethylene Glycol (DEG) is a cost-effective, sweet-tasting industrial solvent commonly used in antifreeze solutions and pharmaceutical products like tooth paste, injectable medications, fever cures, and cough syrup, replacing more expensive compounds like glycerin and propylene glycol. Diethylene glycol (DEG), a substance linked to numerous medication-associated mass poisonings, can pose a significant risk to the kidneys and nervous system when consumed. Ethylene glycol, used in solvents, hydraulic fluids, and antifreezes, can cause health issues like central nervous system depression, cardiac effects, and kidney impairment when consumed in large amounts. Ethylene glycol is a colorless, sweet-tasting substance that is mostly found in antifreeze but is also occasionally used to manufacture industrial solvents. Ingestions, whether intentional or unintentional, are usually the cause of exposures. Intentional exposures might be motivated by the desire to self-intoxicate or by a suicide attempt in the absence of ethanol, although accidental hazardous exposures are more common due to its sweet flavor.

Index Terms-Promethazine, Glycerine, Alteration, Banned, Diethylene Glycol, Ethylene Glycol.

Selection of Antiemetic by Clinical Situation:

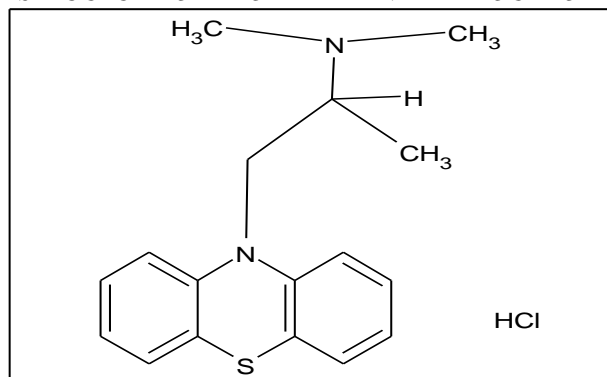
Clinical Situation	Associated Neurotransmitters	Recommended Antiemetic
Vestibular Nausea/Motion Sickness	Histamine, Acetylcholine	Meclizine (Antivert), Scopolamine
Migraine-Associated Nausea	Dopamine	Metoclopramide (Reglan), Prochlorperazine, Promethazine
Gastroenteritis	Dopamine, Serotonin	Promethazine, Serotonin Antagonists
Pregnancy-Induced Nausea	Unknown	Mild:ginger.pyridoxine with or without doxylamine Hyperemesis:corticosteroids,* ondansetron(Zofran)

*Avoid use before 10 weeks gestation because increased risk of oral clefts

I. INTRODUCTION

Methazine, a derivative of phenothiazine, blocks various receptors, including histonegic, cholinergic, muscarinic, and partly doperminergic. Its primary antiemetic activity is in the chemoreceptor trigger zone, potentially leading to excessive sedation. Due to resource constraints, drug costs significantly impact healthcare in underdeveloped nations, with most African countries having easy access to promethazine[1].Promethazine hydrochloride, also known as N,Ndimethyl-1-(10H-phenothiazine-10-yl)propan2-amine hydrochloride, is a member of the phenothiazine chemical family and is considered the first class of antihistamine medications.[2] The World Health Organization (WHO) issued a health advisory on October 5 regarding four items, including Promethazine Oral Solution, Promethazine appears to have an antiemetic effect due to its antagonism of central histamine receptors[3]. Promethazine, prochlorperazine, and metoclopramide (Reglan) are examples of dopamine antagonists. They block dopamine stimulation in the chemoreceptor trigger zone, thereby limiting emetic input to the medullary vomiting center. Dopamine antagonists are inexpensive, but have strong antihistamine effects and can cause significant sedation.[4]

STRUCTURE OF PROMETHAZINE HYDROCHLORIDE:



N,N-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine—hydrogen chloride (1/1)

Figure 1: Chemical structure of Promethazine Hydrochloride

Molecular Formula: C₁₇H₂₀N₂S.HCl

Molecular Weight: 320.88

Properties and uses: Promethazine hydrochloride is a crystalline powder that is white or slightly yellowish. It dissolves easily in water, alcohol, and methylene chloride. Both seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis brought on by inhaled allergens and foods, and some milder forms of urticari skin manifestations can all benefit from its use. In addition, it contains some anticholinergic and **SYNTHESIS:**

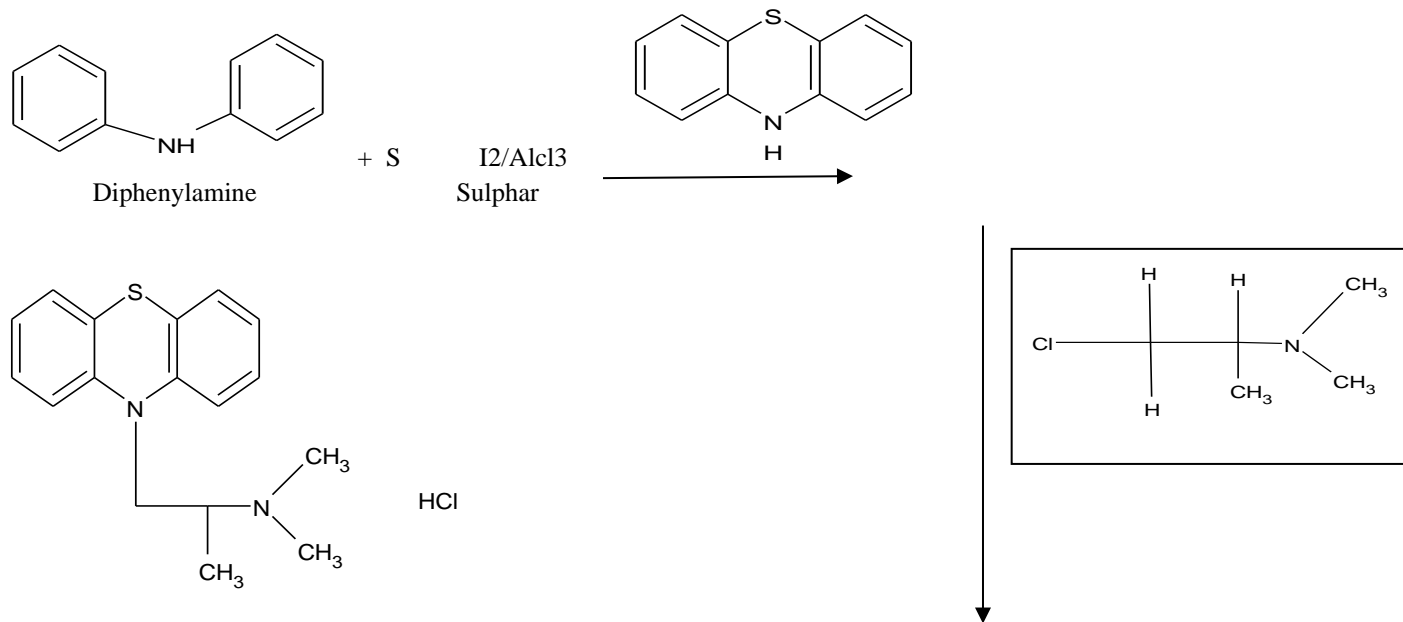
antiserotonergic properties and a potent local anesthetic effect.

Assay: Titrate the sample against 0.1 M sodium hydroxide after dissolving it in a solution of alcohol and 0.01 M hydrochloric acid. Determine the potentiometric end point.

Dose: A daily dose of 20–50 mg is typical.

Dosage forms: Promethazine hydrochloride injection I.P., tablets I.P., B.P., syrup I.P., injection B.P., and oral solution B.P. were all manufactured by the pharmaceutical company Promethazine Hydrochloride.

Melting Point : Melting Point: Approximately 60 °C



N,N-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine—hydrogen chloride (1/1)

(Promethazine Hydrochloride)

Mechanism Of Action:

Promethazine, a phenothiazine chemical, is a first-generation H1 receptor antagonist that blocks histamine H1 receptors without preventing histamine secretion. It is a weak antagonist of dopamine and has an antiemetic effect due to its antagonistic interaction with central histamine receptors.[3] Dopamine antagonists like promethazine, prochlorperazine, and metoclopramide (Reglan) block dopamine stimulation in the chemoreceptor trigger zone, reducing emetic input to the medullary vomiting center. Dopamine antagonists, although inexpensive, can be highly sedative and possess potent antihistamine properties.[4]

Adverse Effects: Promethazine, due to its antidopaminergic effects, may worsen symptoms in Parkinson disease patients, including tardive dyskinesia, akathisia, acute dystonia, and pseudoparkinsonism.[5]

Contraindication: Promethazine hydrochloride should not be given to individuals who are comatose, hypersensitive, or have experienced an unusual reaction to promethazine or other phenothiazines.[6]

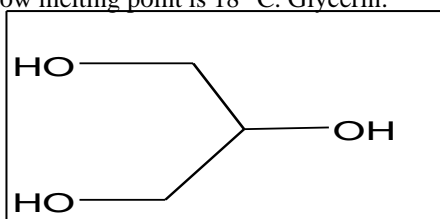
Banned History: Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup, and Magrip N Cold Syrup, manufactured by Maiden Pharmaceuticals Limited in India. Gambia's health officials are investigating a possible link between paracetamol syrup and child deaths due to acute kidney damage. The United Nations health agency found that ethylene glycol and diethylene glycol were present in "unacceptable quantities" in samples of all four products, indicating a drug-related issue.[7]

The WHO has provided technical assistance and advice to Gambia regarding the consumption of DEG or ethylene glycol, warning that their potentially fatal side effects include headaches, nausea, vomiting, diarrhea, difficulty passing urine, altered mental status, and severe renal damage.[7]



Glycerin:

Its low melting point is 18 °C. Glycerin:



propane-1,2,3-triol

Properties :

Glycerol has a specific density of 1.261 g/cm³ and a molecular mass of 92.09382 g/mol.

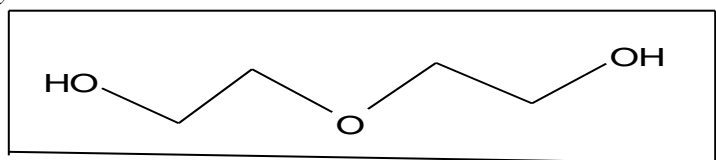
Its high boiling point is 290 °C.

It is a highly hygroscopic, colorless, odorless, viscous, sweet, and non-toxic polyalcohol.

Glycerol is a green solvent used in organic compound hydrogenation reactions, asymmetric reduction reactions, nucleophilic substitution, and Suzuki crosscoupling. It's also suitable for nanoparticle synthesis due to its solubility, toxicity, availability, and chemical reactivity, making it a valuable choice for organic transformations. Glycerol, due to its unique physicochemical properties, has emerged as a versatile green solvent in synthetic organic chemistry and catalysis. [8]Glycerol, often used as a thickening or solvent in cough syrups, has unique lubricating,

soothing, sweetening, and humectant qualities. Its unique characteristics may contribute to the effectiveness of cough syrups in managing severe coughing, rather than just the active components, as discussed in this review. Triglycerides, naturally occurring forms of glycerol, are found in all living cells and fermented foods. Glycerol, discovered in 1984, is a component of dynamite and glue, and is found in suppositories and cough suppressants. Glycerol, a key component in cough syrups, enhances cough treatment effectiveness through its unique properties such as lubrication, demulcency, sweetness, and humectant activity.[9]

Diethylene Glycol:



2,2'-oxydi(ethan-1-ol)

Properties:

Molecular Weight;106.12 g/mol

Description: Diethylene glycol appears as a colorless liquid. Denser than water MayContact can cause minor eye, mucous membrane, and skin irritation. be slightly toxic by ingestion. Used to make other chemicals.

Toxicity of Diethylene Glycol:

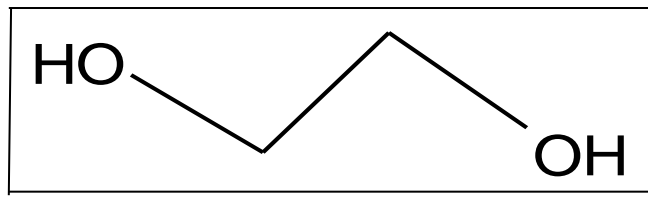
Diethylene glycol (DEG) is used in various products, including lubricants, brake fluids, and cosmetics, but it can cause death, encephalopathy, peripheral neuropathy, renal insufficiency, and coma. Over the past 70 years, at least ten mass poisonings have occurred due to DEG-tainted medications. When used in pharmaceutical products instead of safer diluting

agents like pharmaceutical grade glycerin, contamination occurs.[10] Medical experts warn that accidental replacement of DEG and ethylene glycol with cheaper commercial-grade solvents may lead to contamination due to the compounds' solubility.[7] Seven children in Cape Town died from diethylene glycol poisoning between mid-June and early August 1969, a solvent used in industry with few reported cases.[11]

Another Diethylene Glycol Case Study:

Elixir Sulfanilamide Defeat:In 1937, a Tennessee-based company introduced Sulfanilamide, a liquid form of the popular antibiotic, which caused over 100 deaths. The FDA discovered that the solvent, diethylene glycol, was the cause of death.[12]

Ethylene Glycol:



ethane-1,2-diol

Physical Properties:

chemical formula : C 2 H 6 O 2

Molecular Weight: 62.07 g/mol.

Properties and Uses: Ethylene glycol is a clear, slightly viscous liquid that is completely miscible with water and has no smell, with a vapor pressure of 0.06 mm Hg at 20°C.

Ethylene Glycol Toxicity: Acute ethylene glycol poisoning is a rare but deadly poisoning that can be significantly influenced by early detection and timely treatment. Radiator antifreeze, primarily made of colorless, odorless liquid ethylene glycol, is used in various commercial products and is a significant cause of morbidity and death.[13] Ethylene glycol consumption leads to three acute health effects: cardiopulmonary effects, renal damage, and CNS depression, causing symptoms like vomiting, drowsiness, coma, respiratory failure, convulsions, metabolic changes, and gastrointestinal disturbance.[14]

CONCLUSION

Ethylene glycol and diethylene glycol are highly toxic substances that can cause serious health problems, including death, if ingested. They are often used in industrial and commercial products, such as antifreeze, solvents, and cleaning products. However, they can also be found in some consumer products, such as over-the-counter medications and cough syrups.

Children are particularly vulnerable to ethylene glycol and diethylene glycol poisoning, as they are more likely to accidentally ingest these substances. Even small amounts of ethylene glycol or diethylene glycol can be toxic to children, and even fatal doses can be small.

In 2013, the World Health Organization (WHO) issued a warning about the dangers of ethylene glycol and diethylene glycol poisoning in children. The WHO noted that there have been a number of mass poisonings of children in recent years due to contamination of over-the-counter medications and cough syrups with these substances.

In response to the WHO warning, many countries have banned the use of ethylene glycol and diethylene glycol in certain consumer products, including over-the-counter medications and cough syrups. For example, India banned the use of promethazine syrup

in 2014 after a number of children died from poisoning due to contamination with diethylene glycol and ethylene glycol.

The ban on promethazine syrup is a positive step towards protecting children from ethylene glycol and diethylene glycol poisoning. However, it is important to note that these substances can still be found in other consumer products, such as antifreeze and solvents. It is therefore important to keep these products out of reach of children and to properly dispose of them when they are no longer needed.

In 2022 ,6 th of October the Promethazine Syrup Banned Due to alteration Glycerine by the diethylene glycol and ethylene glycol.

Recommendations

Parents and caregivers should be aware of the dangers of ethylene glycol and diethylene glycol poisoning and take steps to protect their children from exposure to these substances. Keep all products that contain ethylene glycol or diethylene glycol out of reach of children. Properly dispose of products that contain ethylene glycol or diethylene glycol when they are no longer needed. If you suspect that your child has ingested ethylene glycol or diethylene glycol, seek medical attention immediately.

Results:

Promethazine syrup was banned in 2022 due to contamination with diethylene glycol and ethylene glycol. These substances are highly toxic and can cause serious health problems, including death, if ingested. Diethylene glycol and ethylene glycol can alter glycerine by increasing its toxicity. This is because they are both metabolised to oxalic acid, which can damage the kidneys and other organs. the results of this project show that promethazine syrup was banned in India due to contamination with diethylene glycol and ethylene glycol, which can alter glycerine by increasing its toxicity. This contamination posed a serious health risk to consumers, especially children.

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