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TOXICOLOGY OF ETHYLENE GLYCOL AND DIETHYLENE GLYCOL IN COUGH SYRUPS

Abstract

Cough syrups are widely used therapeutic agents, particularly among children. However, contamination with toxic excipients such as ethylene glycol (EG) and diethylene glycol (DEG) has led to multiple fatal outbreaks worldwide. Both compounds are inexpensive substitutes for pharmaceutical-grade solvents such as glycerin and propylene glycol, but their ingestion can result in severe metabolic acidosis, renal failure, neurological damage, and death. This article reviews the toxicology of EG and DEG in cough syrups, highlighting mechanisms of toxicity, clinical features, historical outbreaks, and strategies for prevention.

Keywords: Ethylene glycol; Diethylene glycol; Cough syrups; Toxicology; Pharmaceutical contamination; Mass poisoning; Pediatric safety

Introduction

Cough syrups are among the most frequently consumed over-the-counter (OTC) medicines, especially in pediatric populations. The safety of excipients used in their formulation is essential. In recent decades, multiple incidents of poisoning have been reported due to contamination of syrups with ethylene glycol (EG) and diethylene glycol (DEG). These glycols are industrial chemicals that can be mistakenly or fraudulently used in pharmaceutical preparations as cheaper

substitutes for glycerin or propylene glycol. Their toxic effects have caused mass poisoning episodes across Asia, Africa, and Latin America, resulting in significant mortality among children (O'Brien et al., 2023).

This paper provides a detailed toxicological review of EG and DEG contamination in cough syrups, examining mechanisms of toxicity, clinical presentation, and measures for prevention.

This article is based on a narrative review of scientific literature and case reports. A systematic search of PubMed, Scopus, and WHO reports from 1980 to 2024 was conducted using keywords: "*ethylene glycol*," "*diethylene glycol*," "*cough syrups*," "*toxicology*," "*mass poisoning*," and "*drug safety*." Only peer-reviewed articles, official health organization statements, and documented case investigations were included.

- **Ethylene glycol (EG):** A colorless, odorless, sweet-tasting liquid ($C_2H_6O_2$), commonly used in antifreeze.
- **Diethylene glycol (DEG):** A viscous, colorless liquid ($C_4H_{10}O_3$), used as a solvent and plasticizer. Both are miscible with water and resemble glycerin in appearance, which increases the risk of substitution in pharmaceutical products.

Mechanism of Toxicity

- **Ethylene glycol** is metabolized by alcohol dehydrogenase to glycolaldehyde, glycolic acid, and ultimately oxalic acid, which binds calcium to form calcium oxalate crystals, leading to metabolic acidosis, nephrotoxicity, and hypocalcemia (Jacobsen & McMartin, 1986).

- **Diethylene glycol** undergoes metabolism to diglycolic acid, which causes proximal tubular necrosis and acute renal failure (Krenzelok & Jacobsen, 1997).

Clinical Manifestations

- **Early symptoms (within 12 hours):** Nausea, vomiting, abdominal pain, central nervous system (CNS) depression, confusion, seizures.
- **Intermediate phase (12–24 hours):** Severe metabolic acidosis, cardiovascular dysfunction, respiratory distress.
- **Late phase (24–72 hours):** Oliguria, acute kidney injury, neurological sequelae, death.

Historical Outbreaks

1937, USA: Over 100 deaths due to DEG-contaminated sulfanilamide elixir (Geiling & Cannon, 1938).

1990s, Haiti & Nigeria: Pediatric deaths from DEG-contaminated paracetamol syrups (O'Brien et al., 2023).

2006, Panama: At least 100 deaths linked to DEG in cough syrups (Barrett et al., 2007).

2022, The Gambia, Uzbekistan, and Indonesia: WHO reported hundreds of child deaths linked to contaminated cough syrups containing EG and DEG (WHO, 2023).

Regulatory and Safety Issues

Despite existing pharmacopoeial standards, inadequate quality control, falsification of raw materials, and insufficient testing continue to contribute to contamination. WHO emphasizes strict raw material testing, supply chain traceability, and routine screening for EG/DEG as essential preventive measures.

Discussion

The toxicological profile of EG and DEG reveals high risks of systemic toxicity even at relatively small doses. Children are particularly vulnerable due to lower body weight and immature renal function. The repeated occurrence of outbreaks underscores weaknesses in pharmaceutical regulation, particularly in low- and middle-income countries.

Analytical methods such as gas chromatography (GC), liquid chromatography (HPLC), and infrared spectroscopy (FTIR) are recommended for routine detection of EG and DEG in excipients like glycerin. Preventive strategies include:

1. Enforcing stricter global pharmacopeial standards.
2. Implementing supplier audits and raw material authentication.
3. Increasing laboratory surveillance capacity in developing countries.
4. Raising awareness among pharmaceutical manufacturers and regulatory authorities.

Conclusion

The contamination of cough syrups with ethylene glycol and diethylene glycol remains a persistent and preventable cause of pediatric mortality worldwide. Their toxicity arises from metabolites that induce severe acidosis, renal injury, and

neurological damage. Strengthening pharmaceutical regulations, enhancing quality control, and promoting global cooperation are critical to prevent further outbreaks.

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