The phosphate salt of codeine occurs as white, needle-shaped crystals or white crystalline powder. Chemically designated as 7,8-dehydro-4,5a-dihydroxy-17,18-dihydro-3H-pyran-3-one, codeine phosphate has a molecular weight of 406.37, a molecular formula of C_{18}H_{21}N_{2}O_{3}•H_{3}P_{2}O_{4}•1/2H_{2}O, and the following structural formula:

\[
\text{H}_3\text{P}_2\text{O}_4\text{.C}_18\text{H}_{21}\text{N}_2\text{O}_3\text{.1/2H}_2\text{O}
\]

Promethazine hydrochloride, a phenothiazine derivative, is chemically designated as (1+10)-2-(Dimethylamino)propyl] phenothiazine monohydrochloride.

Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which is freely soluble in water and slightly soluble in alcohol. It has a molecular weight of 331.8, a molecular formula of C_{19}H_{25}ClN_{3}O, and the following structural formula:

\[
\text{C}_{19}\text{H}_{25}\text{ClN}_{3}\text{O}•\text{HCl}
\]

Clinical Pharmacology

Codeine: Narcotic analgesics, including codeine, exert their primary effects on the central nervous system and gastrointestinal tract. The analgesic effects of codeine are due to its central action; however, the precise site of action has not been determined, as of yet. Measurable inhibition of various segments of the spinal cord, but not of actions of the codes used therapeutically are mild, with less sedation, respiratory depression, and miosis, when compared to morphine. It has been postulated that biliary tract pressure, but less than morphine or meperidine. Codeine is less constipating than morphine.

Hypotensive Effects: Codeine may produce orthostatic hypotension in ambulatory patients.

Promethazine: Promethazine, an antihistamine indicated for the treatment of cutaneous pruritus, is not a sedative or a hypnotic. It is rapidly absorbed through the gastrointestinal tract. Clinical effects are apparent within 20 minutes.

Codeine has good antitussive activity, although less than that of morphine at equal doses. It is used in preference to morphine, because side effects are infrequent at the usual antitussive dose of codeine.

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 24 hours. It is metabolized in the liver, largely to inactive metabolites and small amounts of free and conjugated morphine. Negligible amounts of codeine and norcodeine are excreted in the urine. Drowsiness, dizziness, dry mouth, and occasional nausea are the most frequent side effects. Promethazine is an H_{1} receptor blocking agent. In addition to its antihistaminic action, it provides clinically useful sedative effects and reduces the coughing reflex.

Complications: Promethazine is a phenothiazine derivative which differs structurally from the antihistaminic agents by the presence of a thiazine side chain and the absence of an ionization. It is thought that this configuration is responsible for its lack of (1/10 that of chlorpromazine) of depressant properties.

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Codeine is contraindicated in patients with a known hypersensitivity to the drug. Promethazine is contraindicated in comatose states, and in individuals known to be hypersensitive to it or have had an idiosyncratic reaction to promethazine or to other phenothiazines.

Indications and Usage

Promethazine hydrochloride syrup is indicated for the temporary relief of cough and upper respiratory symptoms associated with colds or the common cold.

Contraindications

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population. Codeine is contraindicated for the use in patients with postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

Warnings

Respiratory Depression in Children

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population. Codeine is contraindicated for the use in patients with postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

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Adverse Effects

Promethazine hydrochloride and codeine phosphate has an association with respiratory depression, including fatalities, in young children, particularly in the under-one-year infant whose ability to deal with the drug is not fully developed.

Codiene

Respiratory Depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 3A4 (CYP3A4) or high expression levels). Codeine has also been associated with respiratory depression in healthy adults exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see PRECAUTIONS—Nursing Mothers).

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1 or *1/*2). These individuals may metabolize codeine at an exceptionally high rate and have been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanic, 1 to 5% in Caucasians, 3% in African Americans, and 7% in individuals of Arabian descent. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly, and this can convert codeine at a rate that is associated with respiratory consequences in results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening respiratory depression in response to codeine (see PRECAUTIONS—Nursing Mothers).

In pediatric patients (aged 2 to 12 years) who did not receive codeine, following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

Promethazine hydrochloride, USP and codeine phosphate, USP

Rx only

WARNINGS: Respiratory Depression in Children and Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory Depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 3A4 (CYP3A4) or high expression levels). Codeine has also been associated with respiratory depression in healthy adults exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see PRECAUTIONS—Nursing Mothers).

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the benefits of breastfeeding for both the mother and baby. Caution should be exercised when refeeding a premature newborn to ensure that optimal nutrition and growth are achieved. Nutritional disorders, including malnutrition and kwashiorkor, can occur in newborns if feeding is not appropriately managed. Nutritional disorders can lead to growth retardation, hypoglycemia, hypocalcemia, and other complications.

ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, and respiratory depression. Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, and respiratory depression. Children with the phenotype who are prescribed codeine should be monitored for signs of morphine toxicity in their infants including increased apnea (more than usual), difficulty breathing, feeding difficulties, irritability, vomiting, and diarrhea. Neonates, especially those born to mothers taking codeine, should be assessed for signs of respiratory depression and should be observed closely if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).

Drug Interactions: Codeine: In patients receiving MAO inhibitors, an initial test dose is advised to guard against any excessive narcotic effects or MAO interaction.

Promethazine: Drug Interactions - Promethazine may increase, prolong, or intensify the sedative action of other central-nervous-system-depressant drugs, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, anticholinergics, general anesthetics, tricyclic antidepressants, and tranquilizers; therefore, such drugs should be avoided or administered in reduced doses to patients receiving promethazine HCl. When given concomitantly with promethazine, the dose of barbiturates should be reduced by at least one-half, and the dose of narcotics should be reduced by one-quarter to one-half. Dosage must be individualized. Excessive amounts of promethazine HCl relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear within a few hours after the dose is lowered. If these symptoms persist, the drug should be discontinued.

Epinephrine - Because of the potential for promethazine to reverse epinephrine’s vasopressor effect, epinephrine should NOT be used to treat hypotension associated with promethazine overdose.

Anticholinergic - Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monsanto Oxate Inhibitors (MAO) - Drug interactions, including an increased incidence of adverse reactions, have been reported when some MAO inhibitors and phenoxybenzamine are used concomitantly.

Drug/Laboratory Test Interactions: Because narcotic analgesics may increase biliary tract pressure, the use of liver function tests in the assessment of these levels in the newborn may be unreliable for 24 hours after a narcotic analgesic has been given. The following agents or drugs are contraindicated in patients who are receiving treatment with promethazine hydrochloride.

Promethazine Teratogenic Effects: Pregnancy Category C.

Diazepam may be used to control convulsions. Avoid analeptics, which may cause convulsions.

Geriatric Use: Oxicontin use is generally not recommended only under close supervision to patients with a history of drug abuse or dependence. Dependence: Psychological dependence, physical dependence, and tolerance are seen with these drugs.

Drug Abuse and Dependence: Controlled Substance: Promethazine with codeine syrup is a Schedule V Controlled Substance. Abuse: Codeine is known to be subject to abuse; however, the potential for abuse of codeine appears to be quite low. Even paracetamol does not appear to offer the psychic effects sought by addicts who inject or inhale drugs. Other reported clinical experience does not indicate that the potential for abuse of promethazine is any different from that of earlier reports. Clinical experience has not identified any harmful effects produced by intentional abuse of promethazine.

The treatment of overdose with codeine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence (an inability to awaken or to follow oral commands) and irregularities of heart rate and blood pressure. In infants, the signs and symptoms of codeine overdose may be more apparent than in older children due to maturational differences. In pediatric patients less than 6 years of age, because the combination of codeine and promethazine is not safe. Children are relatively more sensitive to the respiratory depressant effects of codeine. Children with a history of drug abuse or dependence are at increased risk for such adverse effects.

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population (see WARNINGS - Box Warning and Use in Pediatric Patients). Respiratory depression and death have occurred in children with obstructive sleep apnea who received the combination product. The deaths were characterized by excessive somnolence that progressively worsened. Children with a history of drug abuse or dependence are at increased risk for such adverse effects.

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