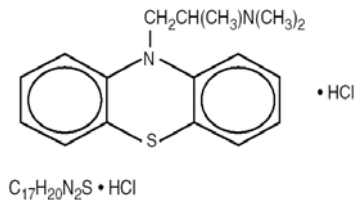


Prothiazine Injection

Chemical Structure



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Description

Promethazine is a phenothiazine however it is not used clinically as a neuroleptic. It is an H₁-antagonist with considerable anticholinergic, sedative and antiemetic effects and some local anesthetic properties.

Promethazine is a versatile drug but is used predominantly as an antiemetic.

Mechanism of Action

The predominant action of promethazine is antagonism of H₁-receptors. Although promethazine is classified as a phenothiazine, its ability to antagonize dopamine is approximately one-tenth that of chlorpromazine. For this reason, promethazine is not used as a neuroleptic. Like other H₁-antagonists, promethazine does not prevent the release of histamine, as do cromolyn and nedocromil, but competes with free histamine for binding at H₁-receptor sites. Histamine receptors in the GI tract, uterus, large blood vessels and bronchial muscle are blocked. The relief of motion sickness and nausea/vomiting appear to be related to central anticholinergic actions and may implicate activity on the medullary chemoreceptor trigger zone. Other CNS receptor sites can also be affected, since promethazine is believed to indirectly reduce stimuli to the brain stem reticular system. Sedation is significant at concentrations achieved from therapeutic dosages. Local anesthetic activity requires higher concentrations than those required to antagonize histamine receptors.

Indications

Amelioration of allergic reactions to blood or plasma. In anaphylaxis as an adjunct to adrenaline and other standard measures after the acute symptoms have been controlled. For other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated. Preoperative, postoperative and obstetric (during labor) sedation. Prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery. For sedation and relief of apprehension and to induce light sleep from which the patient can be easily aroused. Intravenously in special surgical situations, such as repeated bronchoscopy, ophthalmic surgery and poor-risk patients with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia.

Pharmacokinetics

Promethazine injection is administered intramuscularly, and intravenously. Onset of action occurs within 20 minutes after intramuscular administration. Following intravenous administration, onset of action occurs within 3–5 minutes. Antihistaminic and sedative effects are sustained for 4–6 hours and 2–8 hours, respectively. Promethazine is highly protein-bound (80–93%). It is widely distributed in body tissues and fluids, and it crosses the placenta and is excreted into breast milk. Metabolism occurs in the liver, producing inactive metabolites such as promethazine sulfoxide and other glucuronides. The elimination half-life is 10–14 hours, with excretion of metabolites in the urine and the feces.

Dosage and Administration

Promethazine should not be given subcutaneously or intra-arterially.

Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit. The preferred parenteral route of administration for promethazine hydrochloride is by deep intramuscular injection.

Intramuscular injection:

Inject deeply into a large muscle (i.e., upper outer quadrant of the gluteus maximus or lateral part of the thigh). Aspirate prior to injection to avoid injection into a blood vessel.

Intravenous injection:

The 50 mg/ml solution should not be given IV; for IM use only.

Infuse the appropriate dose into the tubing of a free flowing IV solution.

Maximum IV concentration is 25 mg/ml. Further dilution (i.e., to concentrations < 25 mg/ml) may be required to minimize risk of thrombophlebitis. Maximum infusion rate is 25 mg/minute.

For the treatment of nausea/vomiting:

Intramuscular or intravenous dosage:

Adults: 12.5–25 mg every 4–6 hours as needed.

Children ≥ 2 years: 0.25–0.5 mg/kg (max: 25 mg/dose)

every 4–6 hours as needed. According to the manufacturer, the average effective dose is 25 mg.

For the treatment of allergic manifestations:

The average adult dose is 25 mg. This dose may be repeated within 2 hours if necessary; but continued therapy, if indicated, should be via the oral route as soon as circumstances

permit. After initiation of treatment, dosage should be adjusted to the smallest amount adequate to relieve symptoms.

For routine preoperative or postoperative sedation induction, intramuscular or intravenous dosage:

Adults: 25–50 mg as a single dose.

Children \geq 2 years: 12.5–25 mg as a single dose.

To relieve apprehension and induce quiet sleep from which the patient can be easily aroused, intramuscular or intravenous dosage:

Adults: 25–50 mg at bedtime.

Children \geq 2 years: 12.5–25 mg at bedtime.

For sedation in obstetrics:

Intramuscular or intravenous dosage:

Adults: 25–50 mg IM or IV during the early stages of labor and 25–75 mg after labor is established; repeat every 2–4 hours as needed.

Children:

In children under 12 years of age, the dosage should not exceed half that of the recommended adult dosages. As an adjunct to premedication, the suggested dose is 0.9 mg/kg body weight in combination with an equal dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug. Antiemetics should not be used in vomiting of unknown etiology in children.

Patients with renal impairment:

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Contraindications

Phenothiazine derivatives lower the seizure threshold through their effect on GABA; therefore, promethazine should be avoided, if possible, in patients with a seizure disorder or those receiving anticonvulsants. The anticholinergic activity of H1-antagonists may result in thickened bronchial secretions in the respiratory tract, thereby aggravating an acute asthmatic attack or COPD. Although H1-antagonists should be avoided during an acute asthmatic attack, these anticholinergic effects do not preclude the use of H1-antagonists in all asthmatic or COPD patients, particularly if the above respiratory symptom is not a primary component of the illness. Because promethazine exhibits a significant amount of anticholinergic activity, it should be avoided in those who have experienced a worsening in respiratory status due to H1-antagonist therapy. Promethazine is classified as pregnancy category C. H1-antagonists generally are not recommended for use in pregnancy, especially during the third trimester, because of a seizure risk to the fetus. Because there are no adequate studies in pregnant women, promethazine should be considered during pregnancy only when the benefits of therapy outweigh the risks to the fetus. H1-antagonists are not recommended for use during breastfeeding because they can induce a paradoxical CNS

stimulation in neonates or seizures in premature infants.

Inhibition of lactation may also occur. Alternative methods of feeding should be used if promethazine therapy is necessary. Promethazine should be used cautiously in children since a paradoxical CNS stimulation can occur. There have been a number of cases of respiratory depression, sleep apnea and SIDS in children receiving phenothiazine antihistamines. The mechanism of this reaction is not yet known; therefore, promethazine should be used with extreme caution, if at all, in children with a family history of SIDS or sleep apnea. H1-antagonists should not be used in neonates due to the possibility of paradoxical CNS stimulation or seizures. Promethazine should be avoided, if possible, in patients with open-angle or closed-angle glaucoma and an H1- antagonist with less anticholinergic effects should be substituted. An increase in intraocular pressure may occur from the anticholinergic actions of the drug, precipitating an acute attack of glaucoma. Elderly patients are more susceptible to the anticholinergic effects of promethazine, including possible precipitation of undiagnosed glaucoma. Other ocular effects resulting from the anticholinergic effects of promethazine include dry eyes or blurred vision. This may be of significance in the elderly and wearers of contact lenses. Promethazine has substantial anticholinergic effects and a worsening of symptoms may be seen in patients with bladder obstruction, GI obstruction or ileus, benign prostatic hypertrophy or urinary retention. These precautions are most significant when using antihistamines from the ethanolamine or phenothiazine group. The elderly are more susceptible to the anticholinergic effects of drugs since there is a decline in endogenous cholinergic activity that occurs with age. Promethazine is extensively metabolized in the liver. The metabolism of promethazine may be reduced in the presence of hepatic impairment. Those with significant hepatic disease receiving H1-antagonists should be monitored for liver function and side effects. Dosage adjustment may be required in these patients. The quinidine-like local anesthetic and anticholinergic effects of antihistamines are responsible for the adverse cardiac effects which have been observed including tachycardia, ECG changes, hypotension and arrhythmias. Although these cardiovascular effects are uncommon, H1-antagonists should be used conservatively in patients with cardiac disease.

Sulfite sensitivity:

This product contains sodium sulfite and sodium metabisulfite which may cause allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopicnonasthmatic persons.

Interactions

Phenothiazines have been reported to inhibit and reverse the vasopressor effect of epinephrine; therefore, if treatment with a vasopressor agent is necessary in a patient who has been receiving promethazine, norepinephrine should be used.

The anticholinergic activity of MAOIs is minimal; however, anticholinergic effects sometimes occur. It is recommended that the concurrent use of MAOIs with drugs possessing anticholinergic activity be avoided, especially atropine and scopolamine, since their effects and those of other anticholinergic drugs are potentiated and may become severe. Most manufacturers recommend that antihistamines not be used within two weeks of therapy with an MAOI.

Depending on the specific agent, additive anticholinergic effects may be seen when drugs with antimuscarinic properties are used concomitantly with other antimuscarinics. The following drugs are known to possess antimuscarinic properties and should be used together cautiously: atropine and other similar antimuscarinics; some H1-blockers (e.g., carbinoxamine, clemastine, diphenhydramine, methdilazine, promethazine, trimeprazine); some phenothiazines (e.g., mesoridazine, promazine, thioridazine, triflupromazine); some tricyclic antidepressants (e.g., amitriptyline, amoxapine, clomipramine, protriptyline); and other drugs with substantial antimuscarinic properties such as clozapine, cyclobenzaprine and disopyramide. Drugs with minor degrees of anticholinergic effects include amantadine, bupropion, chlorpromazine, doxepin, imipramine, maprotiline, nortriptyline, procainamide and trimipramine. Clinicians should note that antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Because promethazine causes pronounced sedation, an enhanced CNS depressant effect may occur when it is combined with other CNS depressants including ethanol, barbiturates, anxiolytics, sedatives and hypnotics, phenothiazines, opiate agonists or other H1-blockers. A reduction in dosage is recommended during concurrent use.

An increased incidence of extrapyramidal symptoms may occur if promethazine is used concurrently with other agents capable of causing these reactions. Drugs which antagonize dopamine thereby causing EPS reactions include antipsychotics, metoclopramide and amoxapine. Conversely, the effectiveness of dopamine agonists, such as levodopa, amantadine or bromocriptine, may be diminished when given with promethazine due to its blockade of dopamine receptors. Chlorpromazine has been reported to affect control of blood glucose in diabetic patients. It is unclear if phenothiazines directly interact with antidiabetic agents.

Since promethazine is a phenothiazine, it should be used cautiously in patients receiving antidiabetic agents. Concomitant use of antithyroid agents and phenothiazines can increase the risk of developing agranulocytosis. Promethazine should not be used with propylthiouracil. Concurrent use of intrathecal metrizamide with promethazine can lower the seizure threshold. Promethazine should be discontinued at least 48 hours before myelography and not resumed until at least 24 hours afterwards.

Adverse Reactions

H1-antagonists sometimes cause CNS stimulation. This reaction is more likely to occur in children, particularly with a phenothiazine. Symptoms include restlessness, insomnia, palpitations or seizures. Extrapyramidal effects are more likely to be dose-related and may disappear with a reduction in dosage.

Extrapyramidal symptoms (EPS) occur frequently during treatment with phenothiazines and appear to be the result of D2-receptor blockade. These symptoms occur with greater severity and frequency during high-dose therapy. Extrapyramidal symptoms are categorized as dystonic reaction, akathisia (subjective and objective motor restlessness) and parkinsonism. Parkinsonian symptoms are more common in the elderly, whereas children most often develop dystonic reactions, which can be worsened by acute infections or severe dehydration. Dystonic reactions are typically seen during the first week of treatment. Akathisia and parkinsonian symptoms usually develop several days to weeks into therapy. Dystonia and pseudoparkinsonism usually are easily treated with concomitant benztropine, diphenhydramine, lorazepam or amantadine. Akathisia may respond to dosage reduction or concomitant administration of a benzodiazepine (usually lorazepam) or propranolol. In rare patients, an alternate antipsychotic may be necessary.

Neuroleptic malignant syndrome (NMS) can occur in patients receiving phenothiazines. NMS is characterized by hyperthermia, severe extrapyramidal dysfunction, alterations in consciousness, altered mental status, and autonomic instability (sinus tachycardia, low blood pressure or hypertension, diaphoresis). Increased serum creatine phosphokinase (CPK), acute renal failure, and leukocytosis also have occurred. NMS does not appear to be dose-related. Severe cases have resulted in death 3–30 days after the onset of the syndrome. Several predisposing factors may contribute to the development of NMS including heat stress, physical exhaustion, dehydration and organic brain disease. NMS occurs more frequently in young men. The phenothiazine should be immediately discontinued and appropriate supportive therapy initiated as soon as symptoms of NMS are discovered. Hypothermia and hyperthermia have been reported with phenothiazines independent of the neuroleptic malignant syndrome and may be caused by the effect of the phenothiazine on the hypothalamic control of temperature regulation. Hyperpyrexia and heat stroke unrelated to NMS also have occurred.

Tardive dyskinesia (TD) is characterized by involuntary movements of the perioral region (tongue, mouth, jaw, eyelids or face) or choreoathetoid movements in the extremities. It can develop during long-term therapy or following discontinuation of phenothiazine therapy and it is observed more frequently in elderly women. The incidence of TD may be higher in patients with bipolar disorder than with schizophrenia. Some cases can be irreversible. While contradictory evidence exists, it has been suggested that the likelihood of developing TD increases with prolonged treatment and cumulative doses. Although this complication often occurs following prolonged treatment or with administration of high dosages, it also has been reported to occur after short periods of time and with low dosages. Routine monitoring (at 3- to 6-month intervals) of movement disorders is considered the standard practice when using phenothiazines. If signs or symptoms of TD develop, the neuroleptic should be reevaluated and possibly discontinued. Phenothiazines can cause a variety of CNS effects. Drowsiness occurs occasionally during initial treatment with some phenothiazines. Tolerance usually develops with continued therapy. Dizziness may occur as a result of orthostatic hypotension. Other CNS effects reported less frequently include restlessness, insomnia, depression, headache and cerebral edema.

Seizures can occur and are of special significance in patients with preexisting seizure disorders or EEG abnormalities. Anticholinergic effects of phenothiazines include blurred vision, xerostomia, mydriasis, nausea, adynamic ileus, urinary retention, impotence and constipation. These effects can be enhanced by the concomitant administration of anticholinergic antiparkinsonian drugs, antidepressants or other anticholinergic agents. Leukopenia including agranulocytosis is the most common hematologic disturbance that has been reported during phenothiazine administration. Agranulocytosis has occurred rarely and has been associated with combination treatment with other agents. Other hematologic abnormalities that have been associated with phenothiazine therapy include leukocytosis (usually in association with the neuroleptic malignant syndrome), eosinophilia, thrombocytopenia, pancytopenia, aplastic anemia and anemia. Prolonged therapy with phenothiazines can lead to skin hyperpigmentation. Hyperpigmentation generally is restricted to areas of the body exposed to sunlight. Photosensitivity can result and patients should be warned either to keep out of the sun or to use effective sunscreens (SPF 15+) on exposed areas of the body. Withdrawal of the drug can reverse the effects. Contact dermatitis is also possible in predisposed individuals if they come in contact with liquid dosage forms of phenothiazines.

Phenothiazines can cause ocular changes. Pigmentary retinopathy can occur with or without pigmentary changes in the skin during therapy with phenothiazines. Symptoms of blurred vision, difficulty with nighttime vision, or defective color vision should be investigated promptly. Wearing protective dark glasses can reduce the possibility of this reaction. Phenothiazines have been associated with deposition of fine particles in the lens and cornea, which can lead to corneal opacification and visual impairment.

Liver impairment in the form of cholestasis has been reported rarely with administration of phenothiazines. Jaundice is also possible and may even occur in neonates of mothers who received phenothiazines during pregnancy. Cholestatic jaundice from phenothiazines is generally considered a hypersensitivity reaction.

Adverse cardiovascular reactions that have occurred during antipsychotic therapy include hypotension, hypertension, ventricular tachycardia, ECG changes such as QT prolongation and other cardiac arrhythmias such as torsades de pointes. Cardiac arrhythmias such as torsades de pointes secondary to antipsychotic therapy have mainly been associated with thioridazine and haloperidol. Dopamine blockade can lead to hyperprolactinemia. As a result, neuroleptics can cause galactorrhea. Other endocrine changes that can occur during therapy with neuroleptics include amenorrhea or other menstrual irregularity, breast enlargement or mastalgia, libido decrease, impotence, ejaculation dysfunction (no ejaculation) and priapism. Weight gain may also occur during therapy with phenothiazines. Promethazine can cause an injection site reaction. Inadvertant intra-arterial injection can result in arteriospasm, with a possible impairment in circulation and development of gangrene.

Overdosage*Manifestations:*

Hyperexcitability and abnormal movements which have been reported in children following a single administration of promethazine may be manifestations of relative overdosage, in which case, consideration should be given to the replacement of promethazine by other drugs. General signs and symptoms of overdosage range from mild depression of the central nervous and cardiovascular systems, to profound hypotension, respiratory depression and unconsciousness. Stimulation may be evident, especially in children and geriatric patients. Atropine-like signs and symptoms; dry mouth, fixed dilated pupils, flushing, etc. as well as gastrointestinal symptoms may occur.

Treatment:

The treatment of overdosage is essentially symptomatic and supportive. Avoid analeptics, which may cause convulsions. Severe hypotension usually responds to the administration of noradrenaline or phenylephrine. Adrenaline should not be used, since its use in a patient with partial adrenergic blockage may further lower the blood pressure. Extrapyramidal reactions may be treated with anticholinergic antiparkinsonism agents, diphenhydramine or barbiturates. Additional measures include oxygen and intravenous fluids. Limited experience with dialysis indicates that it is not helpful.

Manufacturer:

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