PRESCRIBING INFORMATION

[Pr]Chlorpromazine HCL Inj 25 mg/ml USP

Sterile Antipsychotic–Antiemetic

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Chlorpromazine HCL Inj 25 mg/ml USP

Sterile

THERAPEUTIC CLASSIFICATION

Antipsychotic–Antiemetic

PHARMACOLOGY

The principal pharmacologic effects of chlorpromazine are similar to those of other propylamino derivatives of phenothiazine. Chlorpromazine has strong anticholinergic and sedative effects and moderate extrapyramidal effects. Chlorpromazine has strong antiemetic and adrenergic blocking activity, and weak ganglionic blocking, antihistaminic and antiserotonergic activity.

PHARMACOKINETICS

Chlorpromazine is rapidly absorbed from parenteral sites of injection. Chlorpromazine is extensively metabolized in the liver and is excreted in the urine and bile in the form of numerous active and inactive metabolites; there is evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations following oral administration are much lower than those following intramuscular administration. Moreover, there is very wide intersubject variation in plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect. Although the plasma half-life of chlorpromazine itself has been reported to be only a few hours, elimination of the metabolites may be very prolonged.

Chlorpromazine is very extensively bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placental barrier and are excreted in milk.

INDICATIONS

Chlorpromazine HCL Inj 25mg/ml USP is used for the symptomatic management of psychotic disorders. The drug is also used for the prevention and treatment of nausea and vomiting; for relief of restlessness and apprehension before surgery and for the symptomatic management of the manic phase of bipolar disorder.

CONTRAINDICATIONS

Comatose or depressed states due to CNS depressants; blood dyscrasias; bone marrow depression; liver damage. Hypersensitivity to chlorpromazine; cross-sensitivity to other phenothiazines may occur. Should be avoided in children or adolescents with signs or symptoms suggestive of Reye's Syndrome. Its antiemetic effect may mask the signs and its CNS effect may be confused with the signs of Reye's Syndrome or other encephalopathies.

WARNINGS AND PRECAUTIONS

General

Phenothiazines should be used with caution in patients with cardiovascular disease. Chlorpromazine is an alpha-adrenergic blocking agent and increased pulse rate and transient hypotension have both been reported in some patients receiving these drugs.

Hypotension, which is typically orthostatic, may occur especially in elderly and in alcoholic patients. This effect may be additive with other agents that cause a lowering of blood pressure. If chlorpromazine should cause severe hypotension, most patients will respond to cautious expansion of the vascular volume with sodium chloride. If vasopressor drugs should be needed, the drugs of choice are alpha-receptor agonists such as phenylephrine or methoxamine.

Prolongation of the QT interval, flattening and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving phenothiazines. These changes appear to be reversible and related to a disturbance in repolarization. Give phenothiazines cautiously to patients with heart disease.

Most reported cases of agranulocytosis associated with the administration of phenothiazine derivatives have occurred between the fourth and tenth week of treatment. Therefore, observe patients on prolonged therapy with particular care during that time for the appearance of such signs as sore throat, fever and weakness. If these symptoms appear, discontinue the drug and perform WBC and differential counts.

If bilirubinemia, bilirubinuria or icterus occur, discontinue the drug and perform liver function tests.

Phenothiazines have been associated with retinopathy. Discontinue chlorpromazine if retinal changes are observed.

Use chlorpromazine cautiously in patients with a history of seizures since the drug tends to lower the seizure threshold.

The anticholinergic action of chlorpromazine may be a factor in some cases of intestinal pseudo-obstruction.

Chlorpromazine may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumour.

Contact dermatitis has been reported in nursing personnel; accordingly, the use of gloves when administering chlorpromazine liquid or injectable is recommended.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Although disturbance such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients.

Chlorpromazine may impair sensitivity and adaptation to changes of environmental temperature so that fatal hyperthermia and heat strokes are possible complications.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence; however, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high-dose therapy. Reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

Occupational Hazards: Where patients are participating in activities requiring complete mental alertness such as driving an automobile or operating machinery, administer the phenothiazine cautiously, forewarn the patient and increase the dosage gradually.

Photosensitivity may occur. Patients should utilize sunscreens when exposed to sunlight for significant lengths of time.

Endocrine and Metabolism

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as chlorpromazine. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Special Populations

Pregnant Women

Teratogenic Effects

Safe use of phenothiazines in pregnancy has not been established. Most studies indicate these agents are not teratogenic but there are reports of defects in infants exposed to these drugs during the first trimester. Toxic effects observed after high doses near term include: hypotonia, lethargy, depressed reflexes, paralytic ileus, jaundice, and persistent extrapyramidal syndrome. Therefore, they should be

administered cautiously to women of childbearing potential, particularly during the first trimester of pregnancy and near term.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including chlorpromazine) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Chlorpromazine should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Nursing Woman: Phenothiazines are distributed into milk. Use with caution during lactation because of the possible sedative and anticholinergic side effects to the infant.

Geriatrics: Use in reduced dose. Chlorpromazine may adversely affect many of the conditions commonly occurring in the aged, particularly cardiovascular problems.

Pediatrics: Safety and efficacy of chlorpromazine in children younger than 6 months of age have not been established; the drug should generally not be used in these children unless the condition to be treated is potentially life-threatening. Chlorpromazine should not be used in conditions for which pediatric dosage has not been established.

Phenothiazines may increase the effects of general anesthetics, opiates, barbiturates, alcohol and other CNS depressants as well as atropine and phosphorus insecticides. Phenothiazines may reverse epinephrine's action, thereby cause a further fall in blood pressure. Cross allergenicity with other phenothiazines may occur.

ADVERSE EFFECTS

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

-Fax toll-free to 1-866-678-6789, or

-Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario

K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

In general, members of the dimethylaminopropyl group of phenothiazines have been observed to exert marked sedative effects, and have a definite potential to induce parkinsonian syndrome, cause cholestatic hepatitis with intrahepatic obstructive jaundice, and precipitate dermatological reactions.

Behavioural Reactions: Oversedation; impaired psychomotor function; paradoxical effects, such as agitation, excitement, insomnia, bizarre dreams, aggravation of psychotic symptoms; and toxic confusional states.

CNS: Extrapyramidal reactions, including pseudoparkinsonism (with motor retardation, rigidity, mask-like facies, pill rolling and other tremors, drooling, shuffling galt, etc.); dystonic reactions (including perioral spasms, and trismus, tics, torticollis, oculogyric crises, protrusion of the tongue, difficulty swallowing, carpopedal spasm and opisthotonos of the back muscles); and akathisia. Persistent dyskinesias resistant to treatment have been reported, particularly in elderly patients with previous brain damage. In addition, slowing of the EEG rhythm, disturbed body temperature and lowering of the convulsive threshold have occurred. Dizziness has been reported.

Tardive dyskinesia may appear in some patients on long-term antipsychotic therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. There is no known effective treatment for tardive dyskinesia; antiparkinsonian agents usually do not alleviate the symptoms of this syndrome. All antipsychotic agents should be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptics and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50. Fine vermicular movements of the tongue may be an early sign of the syndrome. If the medication is stopped at that time, the syndrome may not develop. Rarely, a neuroleptic malignant syndrome may occur. Symptoms include unstable pulse and blood pressure, high fever, and coma.

Autonomic Nervous System: Dry mouth, fainting, stuffy nose, photophobia, blurred vision, miosis. Tolerance is developed for most patients. If patients are too much impaired, bethanechol should be given.

Disturbance: Urinary retention, incontinence, priapism.

Gastrointestinal: Anorexia, increased appetite, gastric irritation, nausea, vomiting, constipation, paralytic ileus.

Endocrine System: Altered libido, menstrual irregularities, lactation, false-positive pregnancy tests, inhibition of ejaculation, gynecomastia, and weight gain.

Skin: Itching, rash, hypertrophic papillæ of the tongue, angioneurotic edema, erythema, allergic purpura, exfoliative dermatitis, contact dermatitis, photosensitivity.

Cardiovascular Effects: Hypotension, tachycardia, ECG changes.

Blood Dyscrasias: Agranulocytosis, leukopenia, granulocytopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. Agranulocytosis does not occur in more than 1 in 10,000 patients receiving chlorpromazine.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatic: Jaundice, biliary stasis.

Abnormal Pigmentation: A peculiar skin eye syndrome has been recognized as an adverse effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of skin or conjunctiva and/or discolouration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been

reported. Patients receiving higher doses of phenothiazines for prolonged periods should have periodic complete eye examinations.

Neuroleptic Malignant Syndrome: As with other neuroleptic drug, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of neuroleptic treatment.

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CRC) tested prior to starting chlorpromazine and then periodically throughout treatment.

Miscellaneous: Patients should be advised of the risk of severe constipation during chlorpromazine treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Parkinsonism, acute dystonias, somnolence, seizures, dry mouth, blurred vision, urinary retention, tachycardia, cardiac arrhythmias, hypotension, hypothermia or hyperthermia.

Treatment: Support respiratory and cardiac functions as needed. Maintain fluid and electrolyte balance. Treat hypotension with IV fluids and by placing patients in shock position. If unresponsive, dopamine may be required. Seizures may be treated with IV diazepam. Acute dystonic reactions may be treated with IV diphenhydramine, benztropine or trihexyphenidyl. Hemodialysis is ineffective. Hemoperfusion may be effective in severe cases.

DOSAGE AND ADMINISTRATION

Administration: Chlorpromazine HCL Inj 25mg/ml USP may be administered by deep IM or direct IV injection, or by IV infusion. Direct IV injection is intended for use only during surgery to control nausea and vomiting. Parenteral therapy should be reserved for recumbent patients; however, if cautions are taken to avoid orthostatic hypotension (i.e. patient remains recumbent for at least 30 minutes after injection), acutely agitated ambulatory patients may receive the drug IM.

For IM administration, injection should be made slowly, deep into a large muscle mass such as the upper outer quadrant of the gluteus maximus; if irritation at the IM injection site is a problem, the drug can be diluted with 0.9% sodium chloride injection or 2% procaine hydrochloride. For direct IV injection, Chlorpromazine HCL Inj 25mg/ml USP should be diluted with 0.9% sodium chloride injection to a concentration not exceeding 1 mg/mL and administered at a rate of 1 mg/minute in

adults and 0.5 mg/minute in children. For IV infusion, Chlorpromazine HCL Inj 25mg/mL USP should be added to 500-1000 mL of 0.9% sodium chloride injection and administered slowly.

Dosage: Psychotic Disorders and Excessive Anxiety, Tension, and Agitation.

For the symptomatic management of psychotic disorders in hospitalized patients who are acutely agitated, manic, or disturbed, the usual initial adult IM dose of chlorpromazine is 25 mg. Additional IM doses of 25-50 mg may be given in 1 hour, if necessary. Subsequent IM dosage should be gradually increased over several days to a maximum of 400 mg every 4-6 hours until symptoms are controlled. Usually, patients become quiet and cooperative within 24-48 hours after initiation of therapy; oral therapy should replace parenteral therapy and dosage should be increased until the patient is calm.

The usual initial IM dosage of chlorpromazine for the management of psychotic disorders and behavioural problems in children 6 months of age or older is 0.55 mg/kg every 6-8 hours as necessary. Subsequent dosage may be gradually increased as necessary. Higher dosages (50-100 mg daily) may be necessary in children with severe behaviour disorders or psychotic conditions; older children may require 200 mg daily. There is little evidence that improvement in behaviour in severely disturbed mentally retarded children is further enhanced at oral dosages greater than 500 mg daily. Maximum IM dosage of chlorpromazine in children younger than 5 years of age and in those weighing less than 22.7 kg is 40 mg daily; maximum IM dosage in children 5-12 years of age and weighing 22.7-45.5 kg should not exceed 75 mg daily, except in unmanageable patients.

Nausea and Vomiting

The usual initial adult IM dose of chlorpromazine for the control of nausea and vomiting is 25 mg. If hypotension does not occur, additional IM doses of 25-50 mg may be administered as necessary every 3-4 hours until symptoms subside; oral therapy should then replace parenteral therapy if necessary.

For children 6 months of age or older, the usual initial IM dosage of chlorpromazine for the control of nausea and vomiting is 0.55 mg/kg every 6-8 hours as necessary. Subsequent dosage should be carefully adjusted according to the severity of symptoms and the patient's response. Maximum IM dosage of chlorpromazine in children younger than 5 years of age and in those weighing less than 22.7 kg is 40 mg daily; maximum IM dosage in children 5-12 years of age and weighing 22.7-45.5 kg should not exceed 75 mg daily, except in severe cases.

DESCRIPTION

Chlorpromazine HCL Inj 25mg/ ml USP is a phenothiazine antipsychotic agent.

The solution has a pH of 3-5 and should not be mixed with alkaline media such as atropine or thiopental. The pH of maximum stability is 6.

The hydrochloride salt of chlorpromazine darkens on prolonged exposure to light. The solution must not be used if markedly discoloured or if a precipitate is present.

STORAGE AND STABILITY

Store between 15 and 30^{o}C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Chlorpromazine HCL Inj 25mg/ml USP is a sterile solution of chlorpromazine hydrochloride in water for injection.

Composition:

Each mL of sterile solution for IM or IV use contains: chlorpromazine hydrochloride 25 mg, ascorbic acid 2 mg, sodium bisulfite 1 mg, sodium sulfite 1 mg, sodium chloride 6 mg, water for injection.

Packaging:

Amber ampoules of 2 mL, boxes of 10.