PERIDOL

Tablets

Composition

Each tablet contains:

Haloperidol	5 mg

Action

Although the complex mechanism of the therapeutic effect of haloperidol is not clearly established, it is known that it produces a selective effect on the central nervous system by competitive blockade of postsynaptic dopamine (D_2) receptors in the mesolimbic dopaminergic system, and an increased turnover of brain dopamine to produce its tranquillizing effects. With subchronic therapy, depolarization blockade, or diminished firing rate of the dopamine neurone (decreased release) along with D_2 postsynaptic blockade, results in the antipsychotic action. Blockade of dopamine receptors in the nigrostriatal dopamine pathway produces extrapyramidal motor reactions; blockade of dopamine receptors in the tuberoinfundibular system decreases growth hormone release and increases prolactin release by the pituitary. There is also some blockade of alpha-adrenergic receptors of the autonomic system.

Pharmacokinetics

Absorption

Haloperidol is rapidly absorbed from the gastrointestinal tract following oral administration but appears to undergo first-pass metabolism in the liver. Peak plasma levels of haloperidol occur within two to six hours of oral administration.

Distribution

Haloperidol is approximately 92% bound to plasma proteins. The distribution of haloperidol into the human body tissues and fluids has not been fully determined. In animal studies, the medicine is mainly distributed into the liver, with lower concentrations being distributed into the brain, lungs, kidneys, spleen, and heart. Haloperidol is distributed into breast milk.

Metabolism

Metabolism of haloperidol occurs in the liver. Haloperidol is metabolised by oxidative *N* -dealkylation of the piperidine nitrogen to form flurophenylcarbonic acids and piperidine metabolites that appeared to be inactive, and by reduction of the butyrophenone carbonyl to the carbinol, forming the alcohol hydroxyhaloperidol. Limited data suggest that the reduced metabolite, hydroxyhaloperidol, has some pharmacological activity, although its activity appears to be less than that of haloperidol. There is evidence of enterohepatic recycling and due to the influence of the first-pass effect of metabolism in the liver, plasma concentrations following oral administration are lower than those following intramuscular administration. Haloperidol and its metabolites are excreted in the urine, via the bile and in the faeces. The plasma half-life of haloperidol after oral administration ranges from 12 to 38 hours. Studies have shown that CYP3A4 and/or CYP2D6 are involved in the metabolic biotransformation of haloperidol.

Excretion

The mean plasma half-life (terminal elimination) has been determined as 20.7 ± 4.6 (SD) hours, and although excretion begins rapidly, only 24 to 60% of ingested radioactive medicine is excreted (mainly as metabolites in urine; some in faeces) by the end of the first week, and very small but detectable levels of radioactivity persist in the blood and are excreted for several weeks after dosing. In humans, haloperidol glucuronide is a major metabolite excreted in the urine. About 1% of the ingested dose is recovered unchanged in the urine. The slow excretion may be related to a high degree of plasma protein binding. Haloperidol is highly lipid-soluble and may remain in fatty tissue for some weeks.

Indications

- Management of manifestations of psychotic disorders.
- Control of tics and vocal utterances of Tourette's disorder in children and adults.

Contraindications

- Known hypersensitivity to the drug.
- Patients with severe depression.
- Comatose states
- CNS depression due to alcohol or other CNS depressants.
- Parkinsonism.
- Lesion of the basal ganglia.

Warnings

Lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduction in pulmonary ventilation, especially in elderly patients. If these symptoms appear, remedial therapy should be instituted promptly.

Ambulatory patients should be warned accordingly.

This medication should be used with caution when the following medical problems exist acute drug induced CNS depression, epilepsy, predisposition to glaucoma, hepatic function impairment, hyperthyroidism, thyrotoxicosis, pulmonary insufficiency, renal insufficiency, urinary retention, allergy, history of allergic reaction to drugs.

Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment, and may be potentiated by alcohol.
Therefore, patients should be advised against engaging in potentially hazardous activities requiring mental alertness, such as driving a car or operating machinery, until their susceptibility has been determined.
Hyperpyrexia and heat stroke have been reported with Haloperidol.

Pregnancy
Category C
When given in high doses during late pregnancy, butyrophenone may cause prolonged neurological disturbances in the newborn infant. In pregnant mice, rats and hamsters, administration of haloperidol during the period of organogenesis has produced a range of adverse effects, including embryolethality, gross malformations such as cleft palate and neuronal tube defects, and reduced brain and body weight and behavioral effects in offspring. The significance of these findings for human exposure to therapeutic doses of haloperidol is unknown. Haloperidol should be used during pregnancy only if the anticipated benefit outweighs the risk. The administered dose and duration of treatment should be as low, and as short, as possible.

Nursing Mothers
Haloperidol is excreted in breast milk and is not recommended during breastfeeding. Therefore, if the use of the drug is considered essential, nursing should be discontinued.

Paediatric Use
Haloperidol is not intended for use in children under 3 years of age.

Adverse Reactions

Neurological effects, especially extrapyramidal syndromes, are the most common. Where high dosage treatment is used, extrapyramidal side effects may be encountered at an early stage in the form of dystonic reactions or motor restlessness (akathisia).
Additional CNS disorders reported are insomnia, restlessness, anxiety, and neuroleptic malignant syndrome.
Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes. Corneal and lens opacities have been observed.

Endocrine disorders

Weight gain, lactation, breast engorgement, nastalgia, menstrual irregularities, amenorrhoea, gynecomastia, galactorrhoea, and impotence, inhibition of ejaculation, increased libido, hyperglycemia, hypoglycemia, and hyponatremia.

Dermatologic reactions
Urticaria, exfoliative dermatitis, erythema multiforme, contact sensitivity, maculopapular, and acneiform skin reactions and isolated cases of photosensitivity and loss of hair. A syndrome resembling systemic lupus erythematosus has been reported.

Gastro-intestinal effects
Anorexia, constipation, diarrhoea, hypersalivation, dyspepsia, nausea, and vomiting.

Respiratory effects
Laryngospasm, bronchospasm, and increased depth of respiration.

Cardiovascular effects
Tachycardia, hypotension, hypertension, and ECG changes, particularly Q and T-wave abnormalities, cardiac arrhythmias.

Anti-muscarinic action
Dry mouth, blurred vision, mydriasis, and urinary retention.
Diaphoresis.
Various hematological disorders including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura and a potentially fatal agranulocytosis have been reported less frequently. Agranulocytosis may occur 4 to 10 weeks after starting treatment. Symptoms such as sore throat and fever should be monitored and white cell counts instituted should these symptoms appear.

Withdrawal emergent neurological signs
Some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal.

Other effects include delirium, agitation, and, less frequently, catatonic-like states, insomnia, depression, miosis, EEG changes, convulsions, nasal congestion, and minor abnormalities of liver function tests, and priapism.

Precautions
Since haloperidol is metabolised by the liver, caution is advised in patients with liver disease. It has been reported that seizures can be triggered by haloperidol in known epileptics who were previously controlled. Caution is also advised in conditions predisposing to epilepsy (e.g. alcohol withdrawal and brain damage) or other types of convulsions. Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving antipsychotic medication including haloperidol. Therefore, it should only be used with great caution in patients with hyperthyroidism.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms including nausea, vomiting and insomnia have been described on rare occasions following abrupt cessation of high doses of antipsychotic drugs. Relapse may also occur. Therefore, gradual withdrawal is recommended.

As with all antipsychotic agents, haloperidol should not be used alone where depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist.

If concomitant antiparkinson, is required, it may have to be continued after stopping Peridol (if its excretion is faster than that of haloperidol), in order to avoid the development or aggravation of extrapyramidal symptoms. Physicians should keep in mind the possible increase in intraocular

pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

Haloperidol should be administered cautiously to patients with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Such hypotension should not be treated with epinephrine, since haloperidol may block its vasopressor activity and a paradoxical further lowering of the blood pressure may occur.

Neuroleptic drugs elevate prolactin levels. This elevation persists during chronic administration. Haloperidol should be administered cautiously to patients with previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin level is unknown for most patients.

Drug Interactions

Haloperidol/ Alcohol
Concurrent use may potentiate alcohol intoxication and cause severe hypotension.

Haloperidol/ Amphetamines
Effects of amphetamines may be reduced when used concurrently.

Haloperidol/ Anticholinergics
Physicians should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinsonism agents, are administered concomitantly with haloperidol.

Haloperidol/ Anticoagulants
Concurrent use of anticonvulsants, including barbiturates, may cause a change in the pattern of epileptiform seizures. Dosage adjustment of the anticonvulsant may be necessary. : Rtentiation of anticonvulsant activity does not occur.

Haloperidol/ Antihypertensives
Concurrent use may cause excessive hypotension.

Haloperidol/ Antimuscarinics
Antimuscarinics are sometimes administered concurrently for brief periods to control extrapyramidal effects resulting from haloperidol therapy. However, concurrent use may cause increased intraocular pressure, and may also inhibit the therapeutic effect of haloperidol in schizophrenic patients.

Haloperidol CNS Depressants (including alcohol, hypontics, sedatives and strong analgesics).
Concurrent use may potentiate the depressant activity.

Haloperidol/ Epinephrine
α- adrenergic effects of epinephrine may be blocked, allowing ß- adrenergic effects to predominate when used concurrently with haloperidol, resulting in severe hypotension, Phenylephrine and norepinephrine (levarterenol) have been successfully substituted for epinephrine.

Haloperidol/ Lithium
Concurrent use with haloperidol may cause irreversible neurological toxicity. Patients should be monitored closely for early evidence.

Haloperidol/ Levodopa
Haloperidol may impair the antiparkinson effect of levodopa.

Haloperidol/ Carbamazepine
When prolonged carbamazepine treatment is added to haloperidol therapy, a significant reduction of haloperidol plasma levels is achieved. Therefore, during combination treatment, the haloperidol dose

should be adjusted, when necessary. After stopping carbamazepine, it may be necessary to reduce the dosage of haloperidol.

Haloperidol/ Phenindione
Antagonism of the effect of the anticoagulant phenindione has been reported.

Haloperidol/ Methyldopa
Methyldopa may potentiate the antipsychotic effects of haloperidol or the combination may produce psychosis.

Haloperidol/ Tricyclic Antidepressants
Serum concentrations may be increased by the administration of haloperidol.

Dosage and Administration

There is a considerable variation from patient to patient for medication required for treatment. As with all antipsychotic drugs, dosage should be individualized according to the needs and response of the individual patient. When initiating treatment, consideration should be given to the following factors age of the patient, severity of the disease, history of response to other antipsychotic drugs, concomitant medication or disease state.

Peridol tablets
The recommended initial dose in adults administered 2 or 3 times daily is as follows:

Moderate symptomatology	0.5-2 mg
Severe symptomatology	3-5 mg
Geriatric or debilitated patients	0.5-2 mg
Chronic or resistant patients	3-5 mg

Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Daily doses up to 100 mg may be necessary in some cases to achieve an optimal response.

In children 3-12 years of age (4-15) kg. Body weight), the initial dosage is 0.5 mg/day.

Maintenance dosage
0,025 - 0,05 mg per kg body weight per day in two to three divided doses.
The daily dosage may be increased as needed and tolerated, by 0,5 mg increments at five to seven day intervals up to a maximum of 0,150 mg per kg body weight per day.

Over Dosage

Manifestations
The manifestations of over dosage are an exaggeration of the known pharmacological effects and adverse reactions. The most prominent symptoms are severe extrapyramidal reactions, hypotension and sedation. An extrapyramidal reaction is manifested by muscular rigidity and a generalized or localized tremor, Hypertension, rather than hypotension is also possible. In extreme cases, Patients appear comatose, with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QT-Prolongation, should be considered.

Treatment
There is no specific antidote for haloperidol over dosage. Treatment is largely supportive, but gastric lavage or induction of emesis is recommended in case of oral Haloperidol (unless the patient is bounded, comatose or convulsing), followed by administration of activated charcoal.

For comatose patients, a patent airway should be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration.
ECG and vital signs should be monitored, and monitoring should continue until the ECG normal.
Severe arrhythmias should be treated with appropriate antiarrhythmic measures.

Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin and vasopressor agents such as dopamine or noradrenaline. Adrenaline should not be used, since it might cause profound hypotension in the presence of haloperidol.

In cases of severe extrapyramidal reactions, antiparkinson medication (e.g. benztropine mesylate 1-2 mg I.M. or I.V.) should be administered.

Presentation

Box of 20 tablets