PRODUCT MONOGRAPH

PrAPO-HALOPERIDOL

Haloperidol Tablets
0.5 mg
USP

1 mg, 2 mg, 5 mg and 10 mg
Apotex Standard

Haloperidol Oral Solution USP
2 mg/mL

Antipsychotic

APOTEX INC.
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Toronto Ontario
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Control No: 160968

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ACTION

Apo-Haloperidol (haloperidol) is a butyrophenone derivative with antipsychotic properties that has been considered particularly effective in the management of hyperactivity, agitation and mania. Haloperidol is an effective neuroleptic and also possesses anti-emetic properties; it has a marked tendency to provoke extrapyramidal effects and has relatively weak alpha-adrenolytic properties. It may also exhibit hypothermic and anorexiant effects and potentiates the reaction of barbiturates, general anesthetics and other CNS depressant drugs.

As with other neuroleptics, the mechanism of action of haloperidol has not been entirely elucidated but has been attributed to the inhibition of the transport mechanism of cerebral monoamines, particularly by blocking the impulse transmission in dopaminergic neurons.

Peak plasma levels of haloperidol occur within two to six hours of oral dosing and about 20 minutes after intramuscular administration. The mean plasma (terminal elimination) half-life has been determined at 20.7 ± 4.6 (SD) hours and although excretion begins rapidly, only 24 to 60% of ingested radioactive drug is excreted (mainly as metabolites in urine, some in feces) 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. About 1% of the ingested dose is recovered unchanged in the urine.

INDICATIONS AND CLINICAL USES

Apo-Haloperidol (haloperidol) is indicated in the management of manifestations of acute and chronic psychosis, including schizophrenia and manic states. It may also be of value in the management of aggressive and agitated behaviour in patients with chronic brain syndrome and mental retardation and in the symptomatic control of Gilles de la Tourette's Syndrome.

CONTRAINDICATIONS

Apo-Haloperidol (haloperidol) is contraindicated in comatose states and in the presence of CNS depression due to alcohol or other depressant drugs. It is also contraindicated in patients with significant depressive states, previous spastic diseases and in Parkinson's syndrome, except in the case of dyskinesias due to levodopa treatment. It should not be used in patients shown to be sensitive to the drug, nor in senile patients with pre-existing Parkinson-like symptoms.

Use in Children: Safety and effectiveness in young children have not been established; therefore, haloperidol is contraindicated in this age group.

Use in Pregnancy: Safe use of haloperidol in pregnancy has not been established. It should, therefore, not be used in women of child-bearing potential unless, in the opinion of the physician, the expected benefits of the drug outweigh the potential hazard to the fetus.

WARNINGS AND PRECAUTIONS

Apo-Haloperidol (haloperidol) prolongs the hypnotic action of barbiturates and may potentiate the effects of alcohol and other central nervous system depressant drugs, such as anesthetics and narcotics; caution should therefore be exercised when it is used with agents of this type and adjustments in its dosage may be required.

Haloperidol may lower the convulsive threshold and has been reported to trigger seizures in previously controlled known epileptics. When instituting haloperidol therapy in these patients, adequate anticonvulsant medication should be maintained concomitantly.

Elderly or debilitated patients receiving the drug should be carefully observed for any evidence of oversedation which might lead to dehydration and reduced pulmonary ventilation and could result in complications, such as terminal bronchopneumonia.

Although haloperidol is a relatively non-sedating neuroleptic, sedation may occur in some patients. Therefore, physicians should be aware of this possibility and caution patients about the danger of participating in activities requiring complete mental alertness, judgment and physical coordination, such as driving and operating dangerous machinery.

Haloperidol has been reported to interfere with the anticoagulant properties of phenindione in an isolated case and the possibility should be kept in mind of a similar effect occurring when haloperidol is used with other anticoagulants.

Administration to patients with severe cardiac involvement should be guarded, despite the fact that haloperidol is well tolerated by patients with cardiac insufficiency and that it has been used with favourable results to maintain the cardiovascular function of patients with excitive crises. In very rare instances, it has been felt that haloperidol was contributory to the precipitation of attacks in angina-prone patients. Moderate hypotension may occur with parenteral administration or excessive oral doses of haloperidol; however, vertigo and syncope occur only rarely.

Haloperidol has lowered the level of cholesterol in the serum and liver of monkeys. An accumulation of desmosterol has been observed in the serum of rats given repeated high doses (10 mg/kg) of haloperidol. In man, mild transient decreases in serum cholesterol were reported in preliminary studies. However, in a study involving a group of schizophrenic patients on extended medication, significant lowering of serum cholesterol was not observed with haloperidol and there was no accumulation of desmosterol or 7-dehydrocholesterol. A significant lowering of cholesterol together with an accumulation of another sterol (possibly 7-dehydrocholesterol) has been reported in patients receiving a chemically related drug (trifluperidol) and skin and eye changes (ichthyosis and cataracts) have occurred clinically with another butyrophenone derivative. Skin and eye changes have not been observed in patients receiving haloperidol. However, it is advisable that all patients receiving haloperidol for a prolonged period of time be carefully observed for any changes in the skin and eyes. If such changes are seen, the drug should be discontinued promptly.

Tardive dyskinesias are known to occur in patients on long-term antipsychotic therapy, including haloperidol (see ADVERSE REACTIONS). This should be borne in mind when using neuroleptics, and if possible, the dosage should be reduced or the drug discontinued when manifestations of this syndrome are detected.

The antiemetic action of haloperidol may obscure signs of toxicity due to overdosage of other drugs or mask the symptoms of some organic diseases, such as brain tumor or intestinal obstruction.

If an antiparkinson agent is used concomitantly with haloperidol, both drugs should not be discontinued simultaneously, since extrapyramidal symptoms may occur due to the slower excretion rate of haloperidol.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered to be too limited to be conclusive at this time.

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

Withdrawal Emergent Neurological Signs: Abrupt withdrawal after short-term administration of antipsychotic drugs does not generally pose problems. However, transient dyskinetic signs are experienced by some patients on maintenance therapy after abrupt withdrawal. The signs are very similar to those described under Tardive Dyskinesia, except for duration. Although it is not known whether gradual withdrawal of antipsychotic drugs will decrease the incidence of withdrawal emergent neurological signs, gradual withdrawal would appear to be advisable.

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 haloperidol. 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:

Non-Teratogenic Effects:

Neonates exposed to antipsychotic drugs (including haloperidol) 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.

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

Hematologic:

Venous Thromboembolism:

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including Haloperidol Decanoate, in case reports and/or observational studies. When prescribing Haloperidol Decanoate all potential risk factors for VTE should be identified and preventative measures undertaken.

ADVERSE REACTIONS

Neurological: Neuromuscular (extrapyramidal) effects such as Parkinson-like symptoms, akathisia, dyskinesia, dystonia, hyper-reflexia, rigidity, opisthotonas, and occasionally, oculogyric crisis are the most frequently reported side effects associated with the administration of haloperidol. Headache, vertigo and cerebral seizures have also been reported. The extrapyramidal reactions are usually dose-related in occurrence and severity and as a rule, tend to subside when the dose is reduced or the drug is temporarily discontinued. However, considerable inter-patient variability exists and although some individuals may tolerate higher than average doses of haloperidol, severe extrapyramidal reactions necessitating discontinuation of the drug, may occur at relatively low doses. Administration of an anti-Parkinson agent is usually but not always effective in preventing or reversing neuromuscular reactions associated with haloperidol.

Tardive Dyskinesias: As with all antipsychotic agents, tardive dyskinesia may appear on some patients on long-term 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 they may be accompanied by involuntary movements of extremities.

There is no known effective treatment for tardive dyskinesia; anti-Parkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents 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 neuroleptic drugs 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. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Behavioural: Insomnia, depressive reactions and toxic confusional states are the more common effects encountered. Drowsiness, lethargy, stupor and catalepsy, confusion, restlessness, agitation, anxiety, euphoria and exacerbation of psychotic symptoms, including hallucinations have also been reported.

Cardiovascular: Tachycardia and hypotension have occurred but severe orthostatic hypotension has not been reported. However, should it occur, supportive measures, including intravenous vasopressors such as norepinephrine may be required. EPINEPHRINE SHOULD NOT BE USED, since haloperidol may block the vasoconstrictor effects of this drug.

Autonomic: Dry mouth, blurred vision, urinary retention and incontinence have been reported.

Allergic and Toxic: The overall incidence of significant hematologic changes in patients on haloperidol has been low. Occasionally, there have been reports of mild and usually transient leukopenia and leukocytosis, decreases in blood cell counts, anemia and a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported with the use of haloperidol and then only in associated with other medication. Impairment of liver function (jaundice or hepatitis) has been reported rarely. One case of photosensitization is known and isolated cases of idiosyncratic cutaneous involvement have been observed.

Endocrine: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido and changes in blood sugar levels have been reported.

Gastrointestinal: Heartburn, nausea, vomiting, anorexia, weight loss, constipation, diarrhea and hypersalivation have been reported.

Miscellaneous: Other untoward effects encountered include peripheral edema, hypocholesterolemia, hyperpyrexia, alopecia, laryngospasm, bronchospasm and increased depth of respiration, stasis pneumonia and a syndrome characterized by perspiration, dehydration, hyperthermia and a dazed state of mine (if this occurs the drug should be discontinued).

Patients should be advised of the risk of severe constipation during Apo-Haloperidol treatment, and 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.

In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be 1) severe extrapyramidal reactions, 2) hypotension or 3) sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reaction would be manifest by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akinetic or agitans types respectively.

Gastric lavage or induction of emesis should be carried out immediately followed by administration of the universal antidote. Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma or concentrated albumin and vasopressors agents such as norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions anti-Parkinson medication should be administered.

DOSAGE AND ADMINISTRATION

Initial dosage should be individualized through consideration of severity of symptoms, age, weight, health, previous response to neuroleptic drugs and concomitant disease states. It is important initially to increase dosage adequately until symptoms are controlled or side effects requiring lowering the dosage or discontinuing the drug are encountered when a satisfactory therapeutic response is achieved, dosage should then be reduced gradually to the lowest effective maintenance level.

Patients with previous adverse responses to other euroleptic drugs, children and the elderly or debilitated may require less haloperidol. The optimal response in such patients is best obtained if therapy is initiated at a lower dosage level and titration is more gradual.

Initially, oral dosages of 1-2 mg, b.i.d. or t.i.d. are usually employed, followed by upward adjustment as tolerated until the desired effect is achieved or limiting side effects appear. Clinical experience has shown that it is seldom necessary to employ dosages greater than 4-6 mg t.i.d. However, 30-40 mg daily may be required in severely disturbed patients who remain inadequately controlled by lower doses and up to 100 mg daily has been used occasionally in particularly resistant patients. Nevertheless, the safety of prolonged administration of the higher doses has not been established. After a therapeutic response has been achieved, dosages should be gradually adjusted downwards until a schedule providing adequate maintenance is reached. Maintenance dosages are commonly in the range of 1-2 mg t.i.d. or q.i.d.

Children and Elderly or Debilitated Patients: Lower doses are recommended in these patients since they may be more sensitive to the drug.

Initially daily doses ranging from 0.5 to 1.5 mg (0.25, to 0.5 mg, 2 or 3 times a day) should be employed. Upward adjustment of these doses should be made gradually; maximum and maintenance doses should be individualized and are generally lower in this type of patient.

AVAILABILITY

0.5 mg tablets:	are round, flat-faced with bevelled edges, white tablets, one side scored and engraved “APO” over "0.5”, the other side plain.
1.0 mg tablets:	are round, flat-faced with bevelled edges, yellow tablets, one side scored and engraved "APO” over “1”, the other side plain.

2.0 mg tablets: are round, flat-faced with bevelled edges, pink tablets, one side scored and engraved “APO” over “2", the other side plain.

5.0 mg tablets: round, flat-faced with bevelled edges, green tablets, one side scored and engraved “APO” over “5”, the other side plain.

10.0 mg tablets: round, flat-faced with bevelled edges, light-green tablets, one side scored and engraved "APO”over “10” the other side plain.

Available in bottles of 100, 500 and 1000, and in unit dose packages of 30, 100, 500.

2 mg/mL Oral Solution: A colourless, odourless and tasteless solution containing 2 mg haloperiodol per mL solution.

Available in bottles of 15, 100 and 500 mL.

PHARMACOLOGY

Haloperidol is an anti-psychotic drug with the chemical name 4-(4-(p-chlorophenyl)-4-hydroxypiperidone)-4’-fluorobutyrophenone.

The pharmacological profile of haloperidol in laboratory animals resembles that of the phenothiazine antipsychotics. As with other neuroleptics, it reduces locomotor and exploratory behaviour (ambulation and 'emotional' defecation) in rats at low doses and induces cataleptic immobility and palpebral ptosis at higher doses. Haloperidol is more potent than chlorpromazine in abolishing the righting reflex in mice (milligram potency two times that of chlorpromazine). It also depresses food consumption and weight increase in laboratory animals and has an epileptogenic effect at subtosic dose levels. Haloperidol suppresses the conditioned avoidance response in the jumping box test (milligram potency 16 times that of chlorpromazine in rats). It blocks amphetamine-induced activity in rats and apomorphine-induced emesis in dogs (milligram potency 50 times that of chlorpromazine), but it is weaker than chlorpromazine in prolonging barbiturate sleeping time. It has relatively weak adrenolytic properties. Equal doses of haloperidol and chlorpromazine are required to produce significant hypotension in the cat and hypothermia in the rat. In dogs and cats it decreases the epinephrine-induced contractions of the nictitating membrane but is less effective against norepinephrine. It would appear from studies in the rabbit that the decreased responsiveness of the reticular formation produced by the drug may be more marked in the caudal portion of that area. Changes in the EEG activity produced by haloperidol are similar to those seen with phenothiazine derivatives. In animals and in humans haloperidol is rapidly absorbed following oral administration and peak plasma levels are reached in 2 to 6 hours. Excretion begins promptly but proceeds slowly and in isotope studies small amounts of radioactivity are excreted or can be detected in the plasma several weeks after ingestion of the drug. This may be related to a high degree of plasma protein binding which in one study was observed to the extent of 92%.

TOXICOLOGY

TABLE 1: LD_{50} (mg/kg by ROUTE OF ADMINISTRATION).

SPECIES	I.V	S.C	ORAL
Mice	13	54	144
Rats	22	63	850
Hamsters	-	-	405
Rabbits	8	-	-
Dogs	18	80	90

During an 18 month evaluation in rats haloperidol was mixed with the animal's normal daily diet and consumed in amounts that averaged 33.0, 14.5, 6.5, and 3.5 mg/kg/day. None of these amounts of haloperidol caused abnormalities as evidenced by repeated urinalyses, hematologic studies (CBC and blood chemistries) and gross and/or microscopic observations. At the end of the evaluation however, mean body weights and food consumption were lower in the treated animals than in the untreated controls. The lesser gains in body weight may be attributed to the decreased food consumption; the latter was presumably caused by the drug's tranquilizing action.

Two safety evaluations of haloperidol were conducted in dogs. In one evaluation, three groups of 6 animals each received either 2.0, 0.5 or 0 mg/kg/day for 6 months; in the other evaluation, four groups of 8 animals each received either 12.0, 6.0, 2.0 or 0 mg/kg/day for 12 months.

No fatalities occurred in either evaluation and one of the dogs in the 6 month evaluation exhibited any drug related toxic effects (gross or microscopic). In the 12 months study decreased weight gain was observed in dogs at the mid and high dose levels and dogs on the highest dose showed convulsions, tremors and emesis. Transient breast engorgement and lactation occurred in 6 to 12 female dogs between the third and eighth week of the evaluation but were not dose related. Liver toxicity was dose related with hepatocellular changes seen in dogs on the two highest doses and possibly at all dose levels.

SGPT changes (increase) were reversible since they returned to normal in animals studied for one month after termination of dosing; liver sections from animals sacrificed at this time also indicated that cellular changes had returned toward normal.

When haloperidol was administered to rats (0.6-3.0 mg/kg), rabbits (1.0 and 6.0 mg/kg) and dogs (1.0-4.0 mg/kg), the offspring of each of these species did not exhibit a greater incidence of teratologic effects than was observed in the respective control groups. In rats receiving amounts of the drug (4.0 mg/kg) large enough to produce marked CNS depression, increased delivery time was noted. Available data suggest that in rats, large oral doses (1.9 mg/kg) may reduce libido and that larger i.v. doses (3.0 mg/kg) may decrease implantation. An increased incidence of fetal resorptions was observed in rabbits receiving 6.0 mg/kg orally; however, at 1.0 mg/kg orally this effect was not observed.