PRODUCT MONOGRAPH

Pr DROPERIDOL INJECTION USP

2.5 mg/mL

Neuroleptic - Antiemetic

Sandoz Canada Inc.
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Boucherville, QC, Canada
J4B 7K8

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Droperidol Injection USP
2.5 mg/mL

THERAPEUTIC CLASSIFICATION

Neuroleptic – Antiemetic

CLINICAL PHARMACOLOGY

Droperidol is a butyrophenone derivative and dopamine antagonist with high and preferential affinity for D2 receptors and a slightly lower affinity for α1A adrenergic receptors. Droperidol antagonizes the effects of apomorphine, and its antiemetic effects in the prevention and treatment of PONV have been demonstrated in patients undergoing anaesthesia for a variety of surgical procedures.

No overall respiratory depression has been demonstrated with droperidol, but its co-administration with known respiratory depressants requires monitoring due to individual variation among recipients. The drug has been associated with a dose dependent prolongation of the frequency-corrected QT interval.

The onset of action of a single intramuscular or intravenous dose is rapid, from 3 to 10 minutes following administration, although the peak effect may not be reached until 30 minutes.

Tranquilizing and sedative activity may continue for 2 to 4 hours, alteration of consciousness may last for up to 12 hours, and extrapyramidal symptoms may occasionally last up to 24 hours.

Droperidol inhibits α-adrenergic receptor binding sites and produces direct peripheral vasodilation, which may cause hypotension and decreased peripheral vascular resistance.

Droperidol reduces the pressor effect of epinephrine. It may reduce the incidence of epinephrine-induced arrhythmias, but does not prevent other cardiac arrhythmias.

INDICATIONS AND CLINICAL USE

Droperidol Injection USP is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults and in children (over the age of two years) and adolescents.

Droperidol is not indicated in children under the age of two years as dosage requirements for the safe and effective use of droperidol have not been established for this patient population.

CONTRAINDICATIONS

Droperidol is contraindicated in patients with known or suspected QT prolongation (i.e., QTc interval greater than 440 msec for males or 450 msec for females. This would include patients with congenital long QT syndrome.

Droperidol is contraindicated in patients with known hypersensitivity or intolerance to the drug.

Droperidol should not be used in children 2 years of age and under since safety and efficacy have not yet been established for this patient population.

Droperidol should not be used other than for the prevention and treatment of PONV in patients for whom other treatments are ineffective or inappropriate (see WARNINGS).

WARNINGS

Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving intravenous droperidol. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Injectable droperidol should only be used in the hospital setting, to allow for screening ECGs.

Based on the above-mentioned reports of cases of QT prolongation and serious arrhythmias (e.g., torsades de pointes), all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, cardiac monitoring should start with treatment and be continued for 2 to 3 hours after completing treatment to monitor for arrhythmias.

Droperidol should be administered with extreme caution in the presence of risk factors for development of prolonged QT syndrome, such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinically significant cardiac disease, 3) treatment with Class I and Class III antiarrhythmics, 4) treatment with monoamine oxidase inhibitors (MAOI's), 5) concomitant treatment with other drug products known to prolong the QT interval (see PRECAUTIONS, Drug Interactions), and 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia, or concomitant treatment with drugs (e.g., diuretics) that may cause electrolyte imbalance. Other risk factors may include age over

65 years and alcohol abuse. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

Effects on Cardiac Conduction
A dose-dependent prolongation of the QT interval was observed within 10 minutes of droperidol administration in a study of 40 patients without known cardiac disease who underwent extracranial head and neck surgery. Significant QT prolongation was observed at all three dose levels evaluated, with 0.1, 0.175, and 0.25 mg/kg associated with prolongation of median QTc by 37,44, and 59 msec, respectively.

Cases of QT prolongation and serious arrhythmias (e.g., torsade de pointes, ventricular arrhythmias, cardiac arrest, and death) have been observed during post-marketing treatment with droperidol. Some cases have occurred in patients with no known risk factors and even at low doses. There has been at least one case of nonfatal torsades de pointes confirmed by rechallenge.

Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, cardiac monitoring should be started with treatment and continued for 2 to 3 hours after completing treatment to monitor for arrhythmias.

Use in Pregnancy
The safety of droperidol in pregnancy has not been established; hence, the possible risk to the mother and unborn child should be weighed against the potential benefits before the drug is used. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Droperidol is not recommended for outpatient use, due to prolonged recovery in some cases.

PRECAUTIONS

Other Central Nervous System depressants (e.g. barbiturates, narcotics and other major tranquilizers), given so their actions overlap those of droperidol, must be used in reduced doses (as low as ½ the dose usually recommended) because of additive or possible potentiating effects.

Use with caution in patients with liver or kidney dysfunctions, as these organs are important in the metabolism and excretion of the drug.

Droperidol may precipitate acute manifestations of Parkinson's disease or epilepsy, and should be administered with caution to susceptible patients.

Use in the Elderly
The initial dose of droperidol should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.

Droperidol may cause a vasodilation of peripheral vessels. It should be given with caution to patients receiving vasodilators because it may cause a marked drop in blood pressure. For the same reason, droperidol should be used with extreme caution in hypovolemic patients and care should be taken to replace the blood volume prior to, or at time of anesthesia.

If hypotension occurs, administer parenteral fluid and reposition the patient to improve venous return when operative conditions permit. However, in spinal and peridural anesthesia, tilting the patient into a head-down position may result in a higher level of anesthesia than desired, as well as impair venous return to the heart. To counteract orthostatic hypotension that is not corrected by volume expansion with fluids and other counter-measures, pressor agents other than epinephrine may be used. Epinephrine may paradoxically decrease the blood pressure in patients receiving droperidol, due to the α-adrenergic blocking action of droperidol.

Droperidol may decrease pulmonary arterial pressure, and thus affect interpretation of pulmonary arterial pressure measurements.

Peripheral vasodilation and hypotension from sympathetic blockade in some forms of conduction anesthesia may be complicated by the α-adrenergic blockade of droperidol, and patients receiving this form of anesthesia should be managed appropriately.

Vital signs should be monitored routinely. The EEG, when used postoperatively, may return to normal slowly.

DRUG INTERACTIONS

Potentially Arrhythmogenic Agents: Any drug known to have the potential to prolong the QT interval should not be used together with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as class I or III antiarrhythmics, antihistamines that prolong the QT interval, antimalarials, calcium channel blockers, neuroleptics that prolong the QT interval and antidepressants.

Caution should be used when patients are taking concomitant drugs known to induce hypokalemia or hypomagnesemia as they may precipitate QT prolongation and

interact with droperidol. These would include diuretics, laxatives and supraphysiological use of steroid hormones with mineralocorticoid potential.

CNS Depressant Drugs: Other CNS depressant drugs (e.g., barbiturates, tranquilizers, opioids and general anesthetics) have additive or potentiating effects with droperidol. Following the administration of droperidol, the dose of other CNS depressant drugs should be reduced.

When droperidol is administered with a narcotic analgesic such as fentanyl citrate, the widely differing durations of action should be noted; in addition, RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA. Bradycardia resulting from fentanyl use may be treated with atropine.

ADVERSE REACTIONS

QT interval prolongation, torsades de pointes, cardiac arrest, and ventricular tachycardia have been reported in patients treated with droperidol. Some of these cases were associated with death. Some cases occurred in patients with no known risk factors, and some were associated with low droperidol doses.

Physicians should be alert to palpitations, syncope, or other symptoms suggestive of episodes of irregular cardiac rhythm in patients taking droperidol and promptly evaluate such cases (see WARNINGS, Effects on Cardiac Conduction).

Mild to moderate hypotension and tachycardia may occur immediately following the use of droperidol, especially after rapid administration, but are usually followed by a quick return to the pre-drug levels. If hypotension persists and is severe, the possibility of hypovolemia should be considered and proper fluid replacement instituted if indicated. Administration of droperidol to patients with hypovolemia may result in a dramatic drop in blood pressure and development of serious sequela.

A low incidence of extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) has been observed. Dyskinesia involving the muscles of the pharynx may lead to breathing or swallowing difficulties. Extrapyramidal symptoms can be controlled or reversed with an antiparkinsonian agent. Rare hallucinatory episodes (possibly emergence delirium) have been observed postoperatively. Excitement and restlessness followed the administration of droperidol in a small proportion of cases; these responded to the administration of fentanyl citrate, or a barbiturate. In some instances, dizziness, chills or shivering, muscle rigidity, nausea, vomiting, retching and postoperative drowsiness and increased bleeding may occur.

The use of droperidol with a narcotic analgesic such as fentanyl citrate can result in respiratory depression, apnea, and muscular rigidity, possibly leading to respiratory arrest. Muscle rigidity, particularly involving muscles of respiration, is related to the speed of injection, and its incidence can be reduced by the use of slow intravenous

injection. Respiratory depression may be managed by the use of assisted or controlled respiration, and, if necessary, by a compatible neuromuscular blocking agent.

When droperidol is administered with parenteral analgesics, elevated blood pressure may develop, possibly due to unexplained alterations in sympathetic activity following large doses or from anesthetic or surgical stimulation during light anesthesia.

Neuroleptic Malignant Syndrome
As with other neuroleptic drugs, 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 and requires symptomatic treatment and immediate discontinuation of neuroleptic treatment.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

An overdosage of droperidol produces effects that are extensions of its pharmacologic actions and may include QT prolongation and serious arrhythmias (e.g. torsades de pointes) (see WARNINGS and PRECAUTIONS). Treatment of droperidol overdosage generally involves symptomatic and supportive care.

In the presence of hypoventilation or apnea, oxygen should be administered and respiration assisted or controlled. A patent airway may be maintained by an oropharyngeal airway or endotracheal tube. The patient should be carefully observed for 24 hours, and body warmth and adequate fluid intake should be maintained. Severe or persistent hypotension should be managed with appropriate parenteral fluid therapy.

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

DOSAGE AND ADMINISTRATION

Dosage should be individualized, taking into consideration age, body weight, physical status, underlying pathological conditions, use of other drugs, type of anesthesia to be used, and the surgical procedure planned. Vital signs and ECG should be monitored routinely prior to treatment and continued for 2 to 3 hours after completing treatment to monitor for arrhythmias.

For intravenous use.

Prevention and treatment of post-operative nausea and vomiting (PONV)

***Adults*:** 0.625 mg to 1.25 mg (0.25 to 0.5 ml)

Elderly: 0.625 mg (0.25 ml)

Renal/hepatic impairment: 0.625 mg (0.25 ml)

Children (over the age of 2 years) and adolescents: 20 to 50 microgram/kg (up to a maximum of 1.25 mg)

Children (below the age of 2 years): Droperidol should not be used (see CONTRAINDICATIONS)

Administration of droperidol is recommended 30 minutes before the anticipated end of surgery. Repeat doses may be given every 6 hours as required. See PRECAUTIONS regarding concomitant use of other CNS depressants and in patients with altered response.

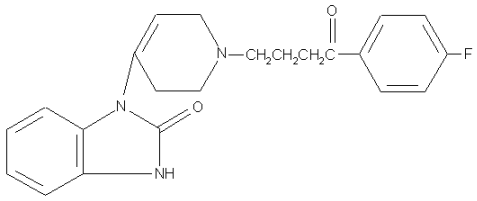
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Droperidol

Chemical Name: 1-(1-[3-p-flurobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl)-2-benzimidazolinone.

Structural Formula:



Molecular Formula: $C_{22}H_{22}FN_3O_2$

Molecular Weight: 379.43

Description: Droperidol is a white to light tan, amorphous or microcrystalline powder with solubilities of approximately 0.1 mg/mL in water and 7.14 mg/mL in alcohol at 25°C. The melting range is 147º-150ºC, and the pKa is 7.64. The pH of a saturated solution at ambient temperature is 7.0. The log-partition coefficient in n-octanol/aqueous buffer at pH 9.6 is 3.47.

COMPOSITION

Droperidol Injection USP is a colourless, sterile, aqueous solution. Each mL contains: 2.5 mg of droperidol, lactic acid and/or sodium hydroxide to adjust pH and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Droperidol Injection USP should be stored between 15 and 30ºC, and protected from light. Discard unused portion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If such abnormalities are observed, the drug should not be administered.

AVAILABILITY OF DOSAGE FORMS

Droperidol Injection USP (2.5 mg/mL) is supplied in 2 mL single use amber vials, boxes of 10, for intramuscular or intravenous injection.

PHARMACOLOGY

Animal Pharmacology

Droperidol did not affect membrane permeability or sodium pump activity in desheathed rabbit vagus; droperidol was a potent reducer of sodium influx during the action potential.

Droperidol has a high affinity for [^{3}H] haloperidol binding sites, but is a relatively weak inhibitor of the dopamine-sensitive adenylate cyclase and of [^{3}H] dopamine binding.

The depressant effect of droperidol on the spontaneous firing of Purkinje cells was relatively quick in onset and termination. There was no depression of spontaneous climbing fibre responses. Droperidol has either a direct action on GABA-receptors or inhibits a specific uptake process for GABA.

Droperidol is a relatively specific cataleptigenic drug with little ptosis-inducing effect. The duration of action of droperidol is relatively short compared with that of haloperidol and chlorpromazine.

In rats, droperidol is an active inhibitor of exploratory ambulation, rearing activity, avoidance habits, and conditioned food intake. Droperidol has weak antiaggressive properties, and does not inhibit the emotional defecation response. Droperidol is a potent antishock agent in rats.

In mice, droperidol prolonged licking reflex in the hot plate test, impaired coordination in the rotarod test, suppressed aggression only at high doses, suppressed righting reflex, and potentiated the action of pentobarbital.

In rats and dogs, droperidol is an antagonist of amphetamines, apomorphine, tryptamine, adrenaline and noradrenaline.

Droperidol reduced the inhibitory effect of carotid sinus nerve stimulation on impulse traffic in afferent chemoreceptor fibres from the carotid body in cats, this may account for the attenuation of fentanyl-induced respiratory depression during concomitant administration.

Cats receiving droperidol 2.5 mg/kg SC showed an average of 25% nictitating membrane relaxation and a 20 mm Hg drop in blood pressure about 30 minutes after injection; these effects lasted for a few hours.

In dogs, droperidol produced immediate depression of the CNS, with reduction in spontaneous motor activity, a loss of responsiveness to environmental sounds, and a tendency to sleep. The effects lasted for 2 hours following the 0.125 mg/kg dose and for more than 6 hours following the 4 mg/kg dose.

In dogs, droperidol was a potent short-acting inhibitor of avoidance responses.

In squirrel monkeys, 0.01 mg/kg or more SC produced sedation, loss of spontaneous motor activity and a state of catalepsy.

Droperidol prevented epinephrine-induced ventricular premature contractions, bigeminal rhythm, and ventricular tachycardia in dogs. Droperidol failed to prevent ouabain-induced ventricular tachycardia in dogs. Droperidol prevented epinephrine-halothane-induced arrythmias in cats. The antiarrythmic activity of droperidol may be due to the reduction of pacemaker activity and the lengthening of the refractory period.

Dogs receiving droperidol showed no change in respiratory volume, a decrease in respiratory rate, and an increase in tidal volume. There was an increase in peripheral blood flow, cardiac output, and heart rate, and a decrease in pulse pressure, central venous-pressure and circulating transit-time.

Renal hemodynamics and renal excretory functions in dogs were not significantly altered, except for an increase in chloride excretion.

Droperidol increased tolerance to digitalis in dogs, whether administered before or after the appearance of digitalis toxicity.

Droperidol produced only a slight degree of hypothermia in rats.

Droperidol has no anticholinergic activity *in vitro* or *in vivo* in several species.

Droperidol has no anticonvulsant activity in mice.

Droperidol has no effect on the diuresis of saline-loaded dogs and rats.

Human Pharmacology
Droperidol exerts tranquilizing or sedative, antiemetic, and cardiovascular effects.

Droperidol, 5 to 10 mg IM, was administered one hour preoperatively to 100 patients undergoing intraocular surgery and 100 patients undergoing stapes surgery. Adequate sedation was achieved in 80% of the patients without the need for supplemental medication. Four patients experienced transient tremor or shivering.

In a double-blind study of droperidol, 55 patients scheduled for varicose vein or hernia surgery were premedicated with 5 mg droperidol PO with atropine, 50 patients were given 10 mg diazepam PO with atropine, and 52 patients were given atropine alone. Anesthesia was then induced with thiopental and maintained with nitrous oxide-oxygen and halothane. Although the droperidol group showed the lowest incidence of nausea on regaining consciousness and on leaving the day-bed unit, the results were not significantly lower until the morning after surgery. There was a significant difference in the amount of analgesic requested postoperatively, with 54% of the droperidol group demanding analgesic compared with 60% of the diazepam group and 73% of the atropine group.

Droperidol effectively reduced the incidence and severity of postoperative emesis in women who received ether and nitrous oxide-oxygen anesthesia for hysterectomy. Shortly after surgery had begun, 21 patients received 5 mg droperidol (0.5 mL IV and 1.5 mL IM) and 20 patients received saline injections. After 6 postoperative hours, the droperidol group showed a significantly lower incidence of emesis (38%) compared with the control group (70%). Over the first 12 hours, the severity of emetic symptoms was significantly reduced in the droperidol group.

Droperidol protects against hypertension and promotes good tissue perfusion during surgery. Adequate fluid volume will protect against the effects of occasional hypotension or decreased peripheral resistance.

Droperidol may reduce the incidence of epinephrine-induced arrhythmias, but does not affect other cardiac arrhythmias.

In healthy subjects, droperidol exerts minimal cardiovascular effects when given IV in a dose of 15 mg in 5 mg increments over 26 minutes, a mean of 17.5 mg over 5 minutes, or 20 mg in a single dose. There was no depressant effect on the myocardium with any of the dosages.

Patients with mitral valve disease given 10 mg of droperidol IV over 10 minutes experienced a fall in systemic vascular resistance, with no compensatory changes in heart rate and cardiac output. Droperidol rapidly reduced raised pulmonary arterial pressure to normal, potentially leading to erroneous hemodynamic assessments.

In a study to compare the cardiovascular effects of droperidol and diazepam, patients undergoing open heart or major vascular surgery were premedicated with droperidol or diazepam. Two doses of droperidol 2.5 mg were administered to 10 patients and two doses of diazepam 5 mg were administered to 19 patients at 15-minute intervals. Droperidol produced transient increases in heart rate and cardiac output, and a transient decrease in peripheral arterial resistance. Diazepam produced small but significant decreases in arterial blood pressure and heart rate and an increase in peripheral resistance.

Droperidol has a direct effect on the peripheral vascular system. Droperidol produced a transient fall in blood pressure and antagonism of epinephrine and norepinephrine in patients undergoing heart surgery with cardiopulmonary bypass, translumbar aortography or vascular surgery. Droperidol, at doses of 0.15 mg/kg, was administered IV or intra-arterially *via* the oxygenator in bypass patients. Return of pressure in bypass patients was slower, presumably because their cardiac output could not vary. Translumbar aortography patients experienced a fall in blood pressure within 2 to 12 seconds of the start of a twenty-second infusion of droperidol 0.10 mg/kg directly into the aorta. Droperidol 0.15 mg/kg, administered to bypass patients, counteracted the pressor response to norepinephrine 10 to 120 mcg and epinephrine 4 to 40 mcg for up to 10 minutes or more; in some cases, epinephrine caused a depressor response.

Normal patients sensitized by cyclopropane were given infusions of epinephrine just adequate to initiate arrhythmia. Droperidol 0.18 mg/kg administered IV increased the arrhythmic threshold from 9.4 to 16.9 mcg/min. This may be attributable to the hypotensive effect of droperidol, as there was a decrease in systolic, diastolic and mean arterial pressure.

Six patients undergoing oral surgery with halothane experienced several dysrhythmias following administration of 5 to 10 mg droperidol IV; in some patients there were marked falls in systolic pressure.

In another study of oral surgery patients receiving 2.5 mL of 1:200,000 norepinephrine, dysrhythmias occurred in 4 (25%) patients given droperidol 0.1 mg/kg IV 10 minutes before induction, and in 4 (16.7%) of unpremedicated patients. The incidence of dysrhythmias was significantly higher in 12 patients (66.7%) premedicated with IV atropine, which may predispose toward dysrhythmia.

Pharmacokinetics
Following intramuscular and intravenous injection in man, there is a rapid distribution phase with an average half-life of 10 minutes, and an elimination phase with a half-life of 134 ± 13 minutes.

Of the administered radioactivity, 75% appeared in the urine and 22% in the feces, with 50% of the fecal radioactivity being unmetabolized droperidol.

TOXICOLOGY

Acute Toxicity
The LD_{50} in mice is reported to be 125 and 250 mg/kg SC, 20 to 40 mg/kg IV, 70 to 90 mg/kg IP, and 195 mg/kg IM. Droperidol is atoxic PO.

The LD_{50} in rats is reported to be 640 mg/kg SC, 30 mg/kg IV, 700 mg/kg PO, and 104 to 110 mg/kg IM.

The LD_{50} in dogs is 25 mg/kg IV, in rabbits it is 11 to 12.6 mg/kg IV and 97 mg/kg IM; in guinea pigs it is 200 mg/kg IM, and in the newborn rat pup the LD_{50} is 170 mg/kg by intragastric route.

Chronic Toxicity
Rats:
Rats administered up to 3200 mg/kg droperidol PO over 14 days demonstrated no adverse effects.

Rats administered 3 or 12 mg/kg IM daily for 30 days demonstrated a dose-related body weight loss and hemorrhaging at the site of injection.

Rats given 12, 6 or 2 mg/kg IV daily for 30 days showed a dose-related decrease in body weight of the males. One rat died after 3 doses of 12 mg/kg.

Dogs:
Dogs administered 3 or 12 mg/kg IM daily for 30 days showed inflammation at the site of injection.

Dogs given 1, 3 or 10 mg/kg IV daily for 30 days showed dose-related sedations and loss of weight. One male dog died of unknown causes after 6 doses of 10 mg/kg.

Dogs receiving 10 mg/kg SC developed muscular tremors, ataxia, prostration, and general motor incoordination, with complete recovery within 24 to 48 hours.

Reproduction and Teratology
Mutagenic effects in female rats were observed at high oral doses of 160 mg/kg.

Rats receiving doses of up to 7.0 mg/kg PO or SC over 3 successive generations showed no adverse effects. Higher doses produced a decrease in the number of pregnancies and body weight loss of pups, an increase in mortality of dams, an increase in number of resorptions, and no change in litter size.

Female rats receiving 1.2 and 12 mg/kg IV from the 6th to 18th day of pregnancy showed no adverse effects on reproduction.

When droperidol was given to rats during labour, the drug caused an increase in the time of delivery at 3 and 12 mg/kg, but shortened the delivery time at 0.5 and 1.0 mg/kg. Mortality of offspring increased when some dams neglected to remove the placenta from the pups. The percentage of pups weaned was less in the treated groups. There was no effect on litter size or abnormalities.

Bred female dogs receiving 8 mg/dog b.i.d. or 1.6-2.0 mg/kg daily for 56 days showed no change in litter size or abnormalities.

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