

**INJECTION
TABLETS
SUPPOSITORIES**



Composition

Pramin Injection

Each ampoule of 2ml contains:
Metoclopramide hydrochloride 10mg

Pramin Tablets

Each tablet contains:
Metoclopramide hydrochloride 10mg

Pramin Suppositories for Adults

Each suppository contains:
Metoclopramide 20mg

Pramin Suppositories for Children

Each suppository contains:
Metoclopramide 5mg

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Action

The pharmacology of metoclopramide is complex and its mechanism(s) of action has not been fully elucidated. The principle pharmacologic effects of metoclopramide involve the GI tract and CNS.

GI Effects

Metoclopramide has several effects on mechanical activity of GI smooth muscle. At low concentration in vitro, metoclopramide increases the resting tone and phasic contractile activity of GI smooth muscle, while at high concentrations, the drug inhibits mechanical activity. Metoclopramide increases lower sphincter pressure in patients with hiatal hernia with or without associated gastroesophageal reflux and in healthy individuals. Following oral or IV administration of the drug, lower esophageal sphincter pressure generally increases to a greater extent in healthy individuals than in patients with reflux; there appears to be substantial interindividual variation in the effect of metoclopramide on lower esophageal sphincter pressure.

Metoclopramide accelerates gastric emptying and intestinal transit from the duodenum to the ileocecal valve by increasing the amplitude and duration of esophageal contractions, the resting tone of the lower esophageal sphincter, and the amplitude and tone of gastric (especially antral) contractions and by relaxing the pyloric sphincter and the duodenal bulb, while increasing peristalsis of the duodenum and jejunum. Unlike nonspecific cholinergic-like stimulation of upper GI smooth muscle, the stimulant effects of metoclopramide on GI smooth muscle coordinate gastric, pyloric, and duodenal motor activity. Metoclopramide is most effective in patients with reduced antral tone and duodenal activity. Metoclopramide lowers the pressure threshold for occurrence of the peristaltic reflex and enhances the frequency and amplitude of longitudinal muscle contractions. In addition to its ability to enhance motor activity of upper GI smooth muscle, metoclopramide may also increase gastric emptying by inhibiting receptive relaxation of the gastro fundus.

Although metoclopramide has been reported to have little, if any effect on motility of the colon in several studies, there is some evidence that the drug may increase colonic motility. The effect of metoclopramide on motility of the gallbladder has been variable.

The pharmacologic actions of metoclopramide on the upper GI tract are similar to those of cholinergic drugs (e.g., bethanechol); however, unlike cholinergic drugs, metoclopramide does not stimulate gastric, biliary, or pancreatic secretions and does not effect serum gastrin concentration.

Although the exact mechanism of action of metoclopramide is unclear, the effects of metoclopramide on GI motility may be mediated via enhancement of cholinergic excitatory processes at the postganglionic neuromuscular junction; antagonism of nonadrenergic, noncholinergic inhibitory motor nerves (i.e., dopaminergic); and/or a direct effect on smooth muscle.

The effects of metoclopramide on GI motility do not depend on intact vagal innervation but are reduced or abolished by anticholinergic drugs (e.g., atropine) and potentiated by cholinergic drugs (e.g., carbachol, methacholine). These findings suggest that metoclopramide's effects on GI motility may depend in part on intramural cholinergic neurons of smooth muscle that are intact after vagal denervation. Unlike cholinergic

drugs, metoclopramide requires intrinsic neuronal storage sites of acetylcholine to exert its pharmacologic effects. Postsynaptic activity results from metoclopramide's ability to enhance release of acetylcholine from postganglionic cholinergic neurons in the GI tract and to sensitize muscarinic receptors of GI smooth muscle to the actions of acetylcholine.

Metoclopramide does not exhibit anticholinesterase activity and its GI stimulant actions are not affected by ganglionic blocking drugs; however, the sensitization to acetylcholine may be prevented by ganglionic blocking drugs (e.g., hexamethonium).

Metoclopramide is a potent dopamine-receptor antagonist, and some of the actions of metoclopramide on GI smooth muscle may be mediated via antagonism of neurotransmission. Specific dopamine receptors in the esophagus and stomach have been identified; however, it is not known if there is a dopaminergic control system for smooth muscle function in the upper GI tract. In the GI tract, dopamine is principally an inhibitory neurotransmitter. Dopamine decreases the intensity of esophageal contractions, relaxes the proximal stomach, and reduces gastric secretion. Although metoclopramide blocks these inhibitory effects of dopamine, the actual role of dopamine in the peripheral control of GI motility has not been fully elucidated. Since cholinergic mechanisms are responsible for most excitatory motor activity in the GI tract, it appears that metoclopramide's therapeutic effects are principally caused by the drug's cholinergic-like activity; however, antagonism of GI dopaminergic activity may augment metoclopramide's cholinergic-like activity.

Nervous System Effects

Metoclopramide is a potent central dopamine-receptor antagonist. The drug has antiemetic and sedative activity.

Antiemetic Effect

The precise mechanism of antiemetic action of metoclopramide is unclear, but the drug has been shown to directly affect the medullary chemoreceptor trigger zone (CTZ) in the area postrema, apparently by blocking dopamine (e.g., D₂) receptors in the CTZ. Metoclopramide increases the CTZ threshold and decreases the sensitivity of visceral nerves that transmit afferent impulses from the GI tract to the vomiting center in the lateral reticular formation. The drug also enhances gastric emptying, which is believed to minimize stasis that precedes vomiting. It also has been suggested that inhibition of serotonin (i.e., 5-HT₃) receptors, at least when relatively high doses of metoclopramide are used, may contribute to the antiemetic action of the drug. Metoclopramide inhibits the central and peripheral emetic effects of apomorphine, hydergine, and levodopa.

The onset of the pharmacological action of Pramin is 1-3 minutes following an I.V. dose, 10-15 minutes following i.m. administration, and 30-60 minutes after an oral dose. The effect of metoclopramide persists for 1-2 hours, and the plasma half-life of an oral dose is about 4 hours. This is prolonged in patients with impaired renal function. About 85% of the radioactivity of an oral dose appears in the urine within 72 hours, with half appearing as unchanged drug or glucuronide and sulfate conjugates.

Indications

Antiemetic and GI motility stimulation; in adults, treatment of symptomatic GI reflux oesophagitis which did not respond to conventional therapy.

Contraindications

Pramin is contraindicated in patients with known sensitivity or intolerance to its action. It should not be administered to patients with pheochromocytoma because it may induce an hypertensive crisis, probably due to the release of catecholamines from the tumor.

Pramin should not be used whenever stimulation of gastrointestinal motility might be dangerous, such as in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation.

Pramin is also contraindicated in epileptics or patients receiving other drugs likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal symptoms may be increased.

Warnings

Use in Pregnancy

Reproduction studies in small animals at 12-250 times the human dose have revealed no evidence of impaired fertility or significant harm to the fetus. However, there are no well controlled studies in pregnant women. Therefore, this drug should only be used when clearly needed, and when the potential benefits outweigh the unknown potential hazards to the fetus.

Use in Breastfeeding

Metoclopramide readily enters into breast milk and may concentrate to about twice the plasma levels 2 hours post administration. Therefore, it is recommended that nursing be discontinued if Pramin is indicated.

Use in Pediatrics

Metoclopramide should be used with caution in pediatric patients, since the incidence of extrapyramidal reactions is increased in these patients. Extrapyramidal effects, especially dystonic reactions, of metoclopramide are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg/kg/day.

It is recommended that the use of metoclopramide be restricted in patients under 20 years of age to severe intractable vomiting of known cause, chemotherapy- or radiotherapy- induced vomiting, as an aid to gastrointestinal intubation, and in premedication.

Adverse Reactions

The most frequent adverse reactions are drowsiness, restlessness, fatigue, lassitude and diarrhea. These reactions occur in approximately 10% of patients treated and are usually mild, transient and reversible upon drug withdrawal. Other reactions that occur less frequently include dizziness, headache, confusion, nausea, agitation, irritability, constipation, dryness of the mouth, neck pain and rigidity.

Extrapyramidal adverse reactions occur in approximately 1-9% of treated patients. These usually are seen during the first 24-48 hours of treatment. More frequently, these reactions occur in children and young adults, and include dystonic reactions of various types which are not dose-related (e.g. involuntary movement of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of the tongue, bulbar type of speech, trismus. Rarely: stridor and dyspnea, possibly due to laryngospasm) and which respond rapidly to treatment with antiparkinsonism drugs such as biperiden i.m. or diazepam. Parkinsonian-like symptoms may include bradykinesia, tremor, cogwheel rigidity, mask-like facies (see Precautions).

Tardive dyskinesia most frequently is characterized by involuntary movements of the tongue, face, mouth or jaw, and sometimes by involuntary movements of the trunk and/or extremities, movements may be choreoathetotic in appearance (see Precautions).

Motor restlessness (akathisia) may consist of feelings of anxiety, agitation, jitteriness, and insomnia, as well as inability to sit still, pacing, foot tapping. These symptoms may disappear spontaneously or respond to a reduction in dosage.

Depression has been reported but this is rare. Rarely, hallucinations have been reported.

Edema (reversible) has also been reported as an adverse reaction with metoclopramide. This may be due to the effect by metoclopramide of increasing aldosterone levels with resultant retention of salt and water.

Endocrine Disturbances

Galactorrhea, amenorrhea, gynecomastia, impotence secondary to hyperprolactinemia (see Precautions). Fluid retention secondary to transient elevation of aldosterone.

Cardiovascular

Hypotension, hypertension, supraventricular tachycardia, bradycardia and possibly AV block.

Hepatic

Rarely, cases of hepatotoxicity, characterized by such findings as jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential.

Renal

Urinary frequency and incontinence.

Hematologic

A few cases of neutropenia, leukopenia, or agranulocytosis, generally without clearcut relationship to metoclopramide. Methemoglobinemia, especially with overdosage in neonates.

Allergic Reactions

A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.

Miscellaneous

Visual disturbances. Porphyria. Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported. This potentially fatal syndrome is comprised of the symptom complex of hyperthermia, altered consciousness, muscular rigidity and autonomic dysfunction.

Transient flushing of the face and upper body, without alternations in vital signs, following high doses intravenously.

Precautions

The relief provided by Pramin may delay recognition of serious diseases. Therefore, Pramin should not be prescribed until a diagnosis has been made.

Patients should be cautioned against engaging in potentially dangerous activities requiring mental alertness, such as driving a car or operating machinery, for a few hours after the drug has been administered. The same precaution applies to childhood activities such as riding a bicycle or playing near traffic.

There is some evidence that metoclopramide may cause depressive episodes. Decreasing the dose to enable resolution of depression, then increasing the dose gradually may obviate depressive symptoms. Metoclopramide should be given to patients with a prior history of depression only if the expected benefits outweigh the potential risks.

Intravenous Pramin should be administered slowly, as rapid administration may induce a transient but intense feeling of anxiety and restlessness, followed by drowsiness. Pramin elevates prolactin levels that persist during chronic administration. Although the clinical significance of this is not clear, extreme caution should be exercised in patients with elevated serum prolactin levels and/or in patients with known or suspected breast cancer.

Metoclopramide has been reported to induce tardive dyskinesia and dysarthria, especially in geriatric patients. This may develop during administration and/or following discontinuation of use. These effects, although possibly reversible, are extremely distressing and their resolution is often slow. Metoclopramide should be avoided in patients with a preexisting dopaminergic deficiency such as idiopathic parkinsonism. However, signs of parkinsonism may even appear in neurologically-normal patients if higher than recommended doses are administered or renal insufficiency is present. In patients with severe renal function impairment, the dose should be reduced by at least 60% of that normally prescribed. This is particularly important because metoclopramide-induced parkinsonism is resistant to levodopa therapy.

In one study in hypertensive patients, intravenously administered metoclopramide was shown to release catecholamines; hence, caution should be exercised when metoclopramide is used in patients with hypertension.

Giving a promotility drug such as metoclopramide theoretically could put increased pressure on suture lines following a gut anastomosis or closure. Although adverse events related to this possibility have not been reported to date, the possibility should be considered and weighed when deciding whether to use metoclopramide or nasogastric suction in the prevention of postoperative nausea and vomiting.

Drug Interactions

Metoclopramide/Anticholinergics/Narcotic Analgesics

The effects of metoclopramide on gastrointestinal motility are antagonized by anticholinergic drugs and narcotic analgesics.

Metoclopramide/Alcohol/Sedatives/Hypnotics/Narcotics/Tranquilizers

Additive sedative effects may occur when metoclopramide is given in conjunction with alcohol or drugs belonging to the classes in this list.

Metoclopramide/Digoxin/Cimetidine/Penicillin

Metoclopramide may diminish the absorption of these agents from the intestine, thus decreasing their bioavailability.

Metoclopramide/Paracetamol/Acetylsalicylic Acid/

Levodopa/Diazepam/Ethanol/Lithium/Tetracycline/Zopiclone/Cyclosporin

Metoclopramide may enhance the absorption of these agents from the small intestine.

Metoclopramide/Insulin

Because metoclopramide influences the delivery of food to the intestines and thus the rate of absorption, insulin dosage or timing thereof may require adjustment.

Metoclopramide/Succinylcholine

Metoclopramide may increase the neuromuscular blocking effect of succinylcholine.

Dosage and Administration

The daily dosage of Pramin is based on 0.5mg/kg body weight, given in equally divided doses. In normal circumstances, this should not be exceeded. It is particularly important to adhere to this dosage in children and young adults.

The parenteral route (i.m. or i.v.) is recommended if severe symptoms are present. Intravenous injections should be administered slowly over a 1-2 minute period. Intravenous infusions should be administered slowly over a period of not less than 15 minutes.

Pramin tablets should be taken with half a glass of water or other liquid, half an hour before, or one hour after meals.

Use in Patients with Renal or Hepatic Impairment

Since metoclopramide is excreted principally through the kidneys, in those patients whose creatinine is below 40 ml/min, therapy should be initiated at approximately one-half the recommended dosage. Depending upon clinical efficacy and safety considerations, the dosage may be increased or decreased as appropriate.

Digestive Disorders

Pramin Ampoules

Age	Dosage
Adults	1 ampoule of 10mg i.m. or i.v., 1-3 times daily, according to the severity of the condition
Adolescents 15-20 years	½-1 ampoule of 10mg i.m. or i.v., 1-3 times daily
Children 9-14 years	up to ½ ampoule of 10mg i.m. or i.v., 1-3 times daily
5-9 years	up to ¼ ampoule of 10mg i.m. or i.v., 1-3 times daily

Pramin Tablets

Age	Dosage
Adults	1 tablet, 3-4 times daily
Adolescents 15-20 years	½-1 tablet, 2-3 times daily

Suppositories for Adults

1-2 suppositories daily, or as required.

Suppositories for Children

1-2 suppositories daily, starting initially with low doses.

Nausea and Vomiting associated with Diabetic Gastroparesis

1 tablet of Pramin, half an hour before each meal and at bedtime for 2-8 weeks, depending on the response and the likelihood of continued well-being on cessation of treatment.

The initial route of administration depends on the severity of the observable symptoms. If only the earliest manifestations of gastric stasis are present, the oral route is indicated. However, if the symptoms are more severe, i.v. therapy should be instituted (for up to 10 days) until symptoms subside. After 10 days, oral administration should be used for maintenance. Since diabetic gastric stasis is frequently recurrent, Pramin therapy should be reinstated at the earliest manifestation.

Nausea and Vomiting caused by Emetogenic Cancer Chemotherapy

Pramin injection should be diluted in 50ml of a parenteral solution (see Pharmaceutical Precautions). Intravenous infusions should be administered slowly over a period of not less than 15 minutes, half an hour before beginning cancer chemotherapy, and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses.

The initial doses should be 2mg/kg body weight if highly emetogenic drugs such as cisplatin or dacarbazine are used alone or in combination.

For less emetogenic regimens, 1mg/kg body weight per dose may be adequate.

Nausea and Vomiting in Postoperative Conditions

In postoperative conditions such as restoration of gastrointestinal motility in the vagotomy syndrome and/or morphine-induced delay in gastric emptying, the recommended dosages are those listed under Digestive Disorders and should be given intramuscularly near the end of surgery.

Facilitation of Diagnostic Procedures

To Facilitate Small Bowel Intubation

If the tube has not passed the pylorus with conventional maneuvers in 10 minutes, a single dose of Pramin injection (undiluted) may be administered slowly by the intravenous route over a 1-2 minute period. The recommended single dose of Pramin injection is 10mg (adults), 2.5-5mg (children 6-14 years of age) and 0.1mg/kg body weight (children under 6 years of age).

To Aid in Radiological Examinations

In patients where delayed gastric emptying interferes with radiological examination of the stomach and/or small intestine, a single dose of Pramin injection (undiluted) may be administered slowly by the intravenous route over a 1-2 minute period. The recommended single dose of Pramin injection is 10mg (adults), 2.5-5mg (children 6-14 years of age) and 0.1mg/kg body weight (children under 6 years of age).

Overdosage

Manifestations

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions. Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1-4/mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia has not been reported on neonates treated with 0.5 mg/kg/day in divided doses.

Treatment

Anticholinergic drugs, antiparkinsonism drugs or antihistamine drugs with anticholinergic properties may be useful in controlling the extrapyramidal reactions.

Symptoms are generally self-limiting and usually disappear within 24 hours.

Methemoglobinemia can be reversed by the intravenous administration of methylene blue.

Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations.

Pharmaceutical Precautions

Metoclopramide preparations are photosensitive and, therefore, should be stored protected from light.

Metoclopramide injection is compatible for dilution with 5% Dextrose, normal saline, Ringer's Injection and Lactated Ringer's Injection. Diluted solutions of metoclopramide can be maintained in a cool dark place, but not longer than 48 hours.

Presentation

Pramin Injection: 5, 50 ampoules.

Pramin Tablets: 30 tablets.

Pramin Suppositories for Adults: 6 suppositories.

Pramin Suppositories for Children: 6 suppositories.

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