EMESTOP

Ampoule, Tablets & Syrup

Composition

Emestop Injection
Each ampoule of 2 ml contains Metoclopramide hydrochloride 10 mg.

Emestop Syrup
Each teaspoonful (5 ml) contains Metoclopramide hydrochloride 5 mg.

Emestop Tablets
Each tablet contains Metoclopramide hydrochloride 10 mg.

Action

Metoclopramide, a dopamine receptor antagonist, acts both centrally and peripherally. Its antiemetic action is due to a central effect on the chemoreceptor trigger zone-vomiting centre). Peripherally, Emestop stimulates motility of the upper gastrointestinal tract without affecting gastric, biliary or pancreatic secretions. Experimental evidence has suggested that the effect on motility may be associated with enhanced cholinergic excitatory processes at the postganglionic neuromuscular junction, antagonism of non-adrenergic, non-cholinergic (i.e. dopaminergic) inhibitory nerves and/or a direct effect on smooth muscle.

The post-synaptic activity of Metoclopramide appears to result from its ability to enhance acetylcholine release from post-ganglionic neurons in the gastrointestinal tract, and from its ability to sensitize muscarinic receptors of gastrointestinal smooth muscle to the actions of acetylcholine.

Although the major effects of Metoclopramide appear to be cholinergically based, antagonism of gastrointestinal dopaminergic activity might enhance the cholinergic like activity of the drug.
The effect of Emestop is not dependent on intact vagal innervations, but anticholinergic drugs can abolish it.

Metoclopramide increases the tone and amplitude of gastric and especially antral contractions. It relaxes the pyloric sphincter and the duodenal bulb and increases peristalsis of the duodenum and jejunum, resulting in accelerated gastric emptying and intestinal transit. Like phenothiazines and related drugs that are dopamine antagonists, Metoclopramide produces sedation and may produce extrapyramidal reactions. The drug inhibits the central and peripheral effects of apomorphine, induces release of prolactin and causes a transient increase in circulating aldosterone levels. Emestop also increases the resting tone of the lower esophageal sphincter but has little, if any, effect on the colon or the gall bladder.

Pharmacokinetics
Animal studies have shown metoclopramide to bind to plasma protein (13% - 22%), especially plasma albumin. Biotransformation is by the hepatic route.

Metoclopramide has a half life of four to six hours. The onset of action, by oral route of administration, is from 30 to 60 minutes. The duration on action is 1 to 2 hours.

Elimination is by the renal route, approximately 85% of an oral dose appears in the urine as unchanged drug and as sulfate and glucuronide conjugates.

The elimination half-life is about 6 hours.

Renal impairment
The clearance of metoclopramide is reduced by up to 70% in patients with severe renal impairment, while the plasma elimination half-life is increased (approximately 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for a creatinine clearance <10 mL/minute).

Hepatic impairment
In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance.

Indications

Digestive Disorders
Relief of symptoms such as gastrointestinal pain, heartburn, dyspepsia, flatulence, regurgitation in peptic ulcer, reflux esophagitis, gastritis, duodenitis, hiatus hernia, cholelithiasis post-cholecystectomy dyspepsia, post-anaesthetic vomiting, vomiting due to anti-migraine therapy and intolerance to drugs.

Nausea and Vomiting

- Nausea and vomiting associated with diabetic gastroparesis.
- Nausea and vomiting caused by emetogenic cancer chemotherapy.
- Nausea and vomiting in postoperative conditions, e.g. restoration of gastrointestinal motility in the post-vagotomy syndrome and/or in morphine-induced delay in gastric emptying.

Facilitation of Diagnostic Procedures
Enhancement of passage of barium meals and facilitation of duodenal intubation procedures.

Contraindications

- Metoclopramide 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 a hypertensive crisis, probably due to the release of catecholamines from the tumour.
- Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, such as in the presence of gastrointestinal hemorrhage, mechanical obstruction or perforation.
- Metoclopramide 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

Pregnancy
Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers
Metoclopramide readily enters into breast milk and may concentrate to about twice the plasma level 2 hour's post administration. Therefore, it is recommended that nursing be discontinued if Emestop is indicated.

Adverse Reactions

The most frequent adverse reactions are restlessness, drowsiness, fatigue, lassitude, agitation, irritability, constipation, and diarrhea, and urticarial maculopapular rash, dryness of the mouth, methemoglobinemia, neck pain and rigidity. These reactions occur in approximately 10% of patients treated and are usually mild, transient and reversible upon drug withdrawal.

Extrapyramidal adverse reactions occur in approximately 1-9% of treated patients. 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) and which respond rapidly to treatment with antiparkinsonism drugs such as biperiden I.M. or diazepam.

Depression has been reported but this is rare.
Urinary incontinence has also 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.

Precautions

The relief provided by Metoclopramide may delay recognition of serious diseases. Therefore, Metoclopramide 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.

Intravenous Metoclopramide should be administered slowly, as rapid administration may induce a transient but intense feeling of anxiety and restlessness, followed by drowsiness. Care should be exercised in diabetic patients, as drug-induced gastroparesis may lead to premature activity of administered insulins, resulting in hypoglycemia.

Metoclopramide 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 pre-existing 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.

Drug Interactions

Contraindicated combination

Levodopa or dopaminergic agonists and metoclopramide have a mutual antagonism.

Combination to be avoided

Alcohol potentiates the sedative effect of metoclopramide.

Combination to be taken into account

Due to the prokinetic effect of metoclopramide, the absorption of certain drugs may be modified.

Anticholinergics and morphine derivatives

Anticholinergics and morphine derivatives may have both a mutual antagonism with metoclopramide on the digestive tract motility.

Central nervous system depressants (morphine derivatives, anxiolytics, sedative H1 antihistamines, sedative antidepressants, barbiturates, clonidine and related)

Sedative effects of Central Nervous System depressants and metoclopramide are potentiated.

Neuroleptics

Metoclopramide may have an additive effect with other neuroleptics on the occurrence of extrapyramidal disorders.

Serotonergic drugs

The use of metoclopramide with serotonergic drugs such as SSRIs may increase the risk of serotonin syndrome.

Digoxin
Metoclopramide may decrease digoxin bioavailability. Careful monitoring of digoxin plasma concentration is required.

Cyclosporine
Metoclopramide increases cyclosporine bioavailability (Cmax by 46% and exposure by 22%). Careful monitoring of cyclosporine plasma concentration is required. The clinical consequence is uncertain.

Mivacurium and suxamethonium
Metoclopramide injection may prolong the duration of neuromuscular block (through inhibition of plasma cholinesterase).

Strong CYP2D6 inhibitors
Metoclopramide exposure levels are increased when co-administered with strong CYP2D6 inhibitors such as fluoxetine and paroxetine. Although the clinical significance is uncertain, patients should be monitored for adverse reactions.

Dosage and Administration

The daily dosage of Emestop is based on 0.5 mg/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.

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

Digestive Disorders
Emestop Ampoules
Adults
1 ampoule of 10 mg I.M. or I.V., 1-3 times daily, according to the severity of the condition.

Adolescents 15-20 years
1/2 - l ampoule of 10 mg I.M. or I.V. 1-3 times daily

Children 5-14 years
Up to 1/2 ampoule of 10 mg I.M. or I.V., 1-3 times daily

Emestop Tablets
Adults
One tablet, 3-4 times daily.

Adolescents 15-20 years
1/2 -One tablet, 2-3 times daily

Emestop Syrup
Adults
Two teaspoonfuls, 3 or 4 times daily

Adolescents 15-20 years
1-2 teaspoonfuls, 2-3 times daily

Children

5-14 years: 1/2 -1 teaspoonful, 2-3 times daily.
3-5 years: about 40 drop (2 mg), 2-3 times daily.
1-3 years: about 20 drop (1 mg), 2-3 times daily.

Nausea and Vomiting associated with Diabetic Gastroparesis
One tablet of Emestop, 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.

Nausea and Vomiting caused by Emetogenic Cancer Chemotherapy
Emestop injection should be diluted in 50 ml of a parenteral solution .
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 2 mg/kg body weight if highly emetogenic drugs such as cisplatin or dacarbazine are used alone or in combination. For less emetogenic regimens, 1 mg/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.

Facilitation of Diagnostic Procedures
To Facilitate Small Bowel Intubation
If the tube has not passed the pylorus with conventional manoeuvres in 10 minutes, the intravenous route may administer a single dose of Emestop injection (undiluted) slowly over a 1-2 minute period. The recommended single dose of Emestop injection is 10 mg (adults), 2.5-5 mg (children 6-14 years of age) and 0.1 mg/kg body weight (children under 6 years of age).

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

Over Dosage
Manifestations
Symptoms of over dosage may include drowsiness, disorientation and extrapyramidal reactions.

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.

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

Emestop Injection
Box of 5 ampoules.

Emestop Syrup
Bottle of 30 ml.

Emestop Tablets
Box of 20 tablets.