Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See appendix for more information.

HUMAN-LABELED PRODUCTS:

Methyltestosterone Tablets: 10 mg, & 25 mg; *Methitest*® (Global), generic; (Rx, C-III)

Methyltestosterone Buccal Tablets: 10 mg; *Android*® (Valeant), generic; (Rx, C-III)

Methyltestosterone Capsules: 10 mg; *Testred*® (Valeant), *Virilon*® (Star); (Rx, C-III)

METOCLOPRAMIDE HCL

(met-oh-kloe-***pra***-mide) Reglan®

GI PROKINETIC AGENT

Prescriber Highlights

- Stimulates upper GI motility & has antiemetic properties; more potent as an antiemetic than a prokinetic agent
- Contraindications: GI hemorrhage, obstruction or perforation, hypersensitivity
- Relatively contraindicated: Seizure disorders, pheochromocytoma
- Adverse Effects: DOGS: Changes in mentation & behavior, constipation; CATS: Signs of frenzied behavior or disorientation, constipation; HORSES: IV use, severe CNS effects, behavioral changes & abdominal pain; FOALS: Adverse effects less common

Uses/Indications

Metoclopramide has been used in veterinary species for both its GI stimulatory and antiemetic properties. It has been used clinically for gastric stasis disorders, gastroesophageal reflux, to allow intubation of the small intestine, as a general antiemetic (for parvovirus, uremic gastritis, etc.), and an antiemetic to prevent or treat chemotherapy-induced vomiting.

Pharmacology/Actions

The primary pharmacologic effects of metoclopramide are associated with the GI tract and the CNS. In the GI tract, metoclopramide stimulates motility of the upper GI without stimulating gastric, pancreatic or biliary secretions. While the exact mechanisms for these actions are unknown, it appears that metoclopramide sensitizes upper GI smooth muscle to the effects of acetylcholine. Intact vagal innervation is not necessary for enhanced motility, but anticholinergic drugs will negate metoclopramide's effects. Gastrointestinal effects seen include increased tone and amplitude of gastric contractions, relaxed pyloric sphincter, and increased duodenal and jejunal peristalsis. Gastric emptying and intestinal transit times can be significantly reduced. There is little or no effect on colon motility. Additionally, metoclopramide will increase lower esophageal sphincter pressure and prevent or reduce gastroesophageal reflux. The above actions evidently give metoclopramide its local antiemetic effects.

In the CNS, metoclopramide apparently antagonizes dopamine at the receptor sites. This action can explain its sedative, central anti-emetic (blocks dopamine in the chemo-receptor trigger zone), extrapyramidal, and prolactin secretion stimulation effects.

Pharmacokinetics

Metoclopramide is absorbed well after oral administration, but a significant first-pass effect in some human patients may reduce systemic bioavailability to 30%. There apparently is a great deal of interpatient variation with this effect. Bioavailability after intramuscular administration has been measured to be 74–96%. After oral dosing, peak plasma levels generally occur within 2 hours.

The drug is well distributed in the body and enters the CNS. Metoclopramide is only weakly bound to 13–22% of plasma proteins. The drug also crosses the placenta and enters the milk in concentrations approximately twice those of plasma.

Metoclopramide is primarily excreted in the urine in humans. Approximately 20–25% of the drug is excreted unchanged in the urine. The majority of the rest of the drug is metabolized to glucuronidated or sulfated conjugate forms and then excreted in the urine. Approximately 5% is excreted in the feces. The half-life of metoclopramide in the dog has been reported to be approximately 90 minutes.

Contraindications/Precautions/Warnings

Metoclopramide is contraindicated in patients with GI hemorrhage, obstruction or perforation, and in those hypersensitive to it. It is relatively contraindicated in patients with seizure disorders. In patients with pheochromocytoma, metoclopramide may induce a hypertensive crisis.

Adverse Effects

In dogs, the most common (although infrequent) adverse reactions seen are changes in mentation and behavior (motor restless and hyperactivity to drowsiness/depression). Cats may exhibit signs of frenzied behavior or disorientation. Both species can develop constipation while receiving this medication.

In adult horses, IV metoclopramide administration has been associated with the development of severe CNS effects. Alternating periods of sedation and excitement, behavioral changes and abdominal pain have been noted. These effects appear to be less common in foals.

Other adverse effects that have been reported in humans and are potentially plausible in animals include extrapyramidal effects, nausea, diarrhea, transient hypertension, and elevated prolactin levels.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

Metoclopramide is excreted into milk and may concentrate at about twice the plasma level, but there does not appear to be significant risk to nursing offspring.

Overdosage/Acute Toxicity

The oral LD_{50} doses of metoclopramide in mice, rats, and rabbits are 465 mg/kg, 760 mg/kg and 870 mg/kg, respectively. Because of the high dosages required for lethality, it is unlikely an oral overdose will cause death in a veterinary patient. Likely clinical signs of overdosage include sedation, ataxia, agitation, extrapyramidal effects, nausea, vomiting, and constipation.

There is no specific antidotal therapy for metoclopramide intoxication. If an oral ingestion was recent, the stomach should be emptied using standard protocols. Anticholinergic agents (diphenhydramine 2.2 mg/kg IV, benztropine, etc.) that enter the CNS may be helpful in controlling extrapyramidal effects. Peritoneal dialysis or hemodialysis is not thought to be effective in enhancing the removal of the drug.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving oral metoclopramide and may be of significance in veterinary patients:

- **ANESTHETICS:** If metoclopramide is used concurrently IV, acute hypotension has been reported
- **ATROPINE** (and related anticholinergic compounds): May antagonize the GI motility effects of metoclopramide
- **CHOLINERGIC DRUGS** (*e.g.*, **bethanechol**): May enhance metoclopramide's GI effects
- **CNS DEPRESSANTS** (*e.g.*, **anesthetic agents**, **antihistamines**, **phenothiazines**, **barbiturates**, **tranquilizers**, **alcohol**, etc.): Metoclopramide may enhance CNS depressant effects
- **CYCLOSPORINE**: Metoclopramide increase the rate and extent of GI absorption
- **OPIATE ANALGESICS**: May antagonize the GI motility effects of metoclopramide
- **MAO INHIBITORS** (including **amitraz** and potentially, **selegiline**): Could cause hypertension
- **PHENOTHIAZINES** (*e.g.*, **acepromazine**, **chlorpromazine**, etc.) and **BUTYROPHENONES** (*e.g.*, **droperidol**, **azaperone**): May potentiate the extrapyramidal effects of metoclopramide. The CNS effects of metoclopramide may be enhanced by other sedatives, tranquilizers, and narcotics.
- **TETRACYCLINES**: Metoclopramide increase the rate and extent of GI absorption

Doses

- **DOGS:**

  As an antiemetic:

  a) 0.1–0.4 mg/kg q6h PO, SC or IM; or 1–2 mg/kg/day as a continuous IV infusion (Washabau and Elie 1995)

  b) 0.22–0.55 mg/kg q8h parenterally; constant IV infusion of 1.1–2.2 mg/kg in 24 hours seems to be more effective than intermittent bolus therapy (Hall 2000)

  c) For bilious vomiting syndrome: 0.2–0.4 mg/kg PO once daily given late in the evening (Hall and Twedt 1988)

  d) To help prevent vomiting in patients with laryngeal paralysis and resultant tracheostomy: 0.05 mg/kg SC or slowly IV before small feedings (O'Brien, 1986)

  e) To treat vomiting associated with pancreatitis: 0.01–0.02 mg/kg/hr IV as a CRI or 0.1–0.5 mg/kg IM q8h (Waddell 2007c)

  For disorders of gastric motility:

  a) 0.2–0.4 mg/kg PO three times daily given 30 minutes before meals (Hall and Twedt 1988)

  b) 0.2–0.5 mg/kg PO or SC q8h; give 30 minutes prior to meals and at bedtime for gastro-motility disorders and esophageal reflux (DeNovo 1986)

  c) 0.2–0.5 mg/kg PO q8h PO or parenterally (may be given as a constant rate IV infusion at 0.01–0.02 mg/kg/hr) (Hall and Washabau 2000)

  To increase bladder contractility:

  a) 0.2–0.5 mg/kg PO q8h (Lane 2000)

- **CATS:**

  a) 0.2–0.4 mg/kg PO, SC 3–4 times daily; or as a continuous IV infusion (1–2 mg/kg per day) (Trepanier 1999)

  b) 0.2–0.5 mg/kg q8h PO or parenterally (may be given as a constant rate IV infusion at 0.01–0.02 mg/kg/hr) (Hall and Washabau 2000)

  c) To increase bladder contractility: 0.2–0.5 mg/kg PO q8h (Lane 2000)

- **RABBITS, RODENTS, SMALL MAMMALS:**

  a) Rabbits: 0.2–1 mg/kg PO or SC q6–8h (Ivey and Morrisey 2000)

  b) Rabbits: To assist in removing gastric hairballs: 0.5 mg/kg PO once a day (up to three times a day) (Burke 1999)

  c) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: 0.2–1 mg/kg PO, SC, IM q12h (Adamcak and Otten 2000)

- **HORSES:** (**Note:** ARCI UCGFS Class 4 Drug)

  To stimulate the gastrointestinal tract:

  a) 0.04 mg/kg/hr as a CRI (Lester 2004)

  b) For reflux esophagitis: 0.02–0.1 mg/kg SC q4–12 hours; horses may be prone to the extrapyramidal neurologic side effects of metoclopramide. (Jones and Blikslager 2004)

  b) In foals: 0.02–0.1 mg/kg IM or IV 3–4 times a day (Clark and Becht 1987)

Monitoring

- Clinical efficacy
- Adverse effects

Client Information

- Contact veterinarian if animal develops clinical signs of involuntary movement of eyes, face, or limbs; or develops a rigid posture.

Chemistry/Synonyms

A derivative of para-aminobenzoic acid, metoclopramide HCl occurs as an odorless, white, crystalline powder with pK_as of 0.6 and 9.3. One gram is approximately soluble in 0.7 mL of water or 3 mL of alcohol. The injectable product has a pH of 3–6.5.

Metoclopramide HCl may also be known as: AHR-3070-C, DEL-1267, metoclopramidi hydrochloridum, and MK-745; many trade names are available.

Storage/Stability/Compatibility

Metoclopramide is photosensitive and must be stored in light resistant containers. All metoclopramide products should be stored at room temperature. Metoclopramide tablets should be kept in tight containers.

The injection is reportedly stable in solutions of a pH range of 2–9 and with the following IV solutions: D5W, 0.9% sodium chloride, D5-½ normal saline, Ringer's, and lactated Ringer's injection.

The following drugs have been stated to be physically **compatible** with metoclopramide for at least 24 hours: aminophylline, ascorbic acid, atropine sulfate, benztropine mesylate, chlorpromazine HCl, cimetidine HCl, clindamycin phosphate, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, dimenhydrinate, diphenhydramine HCl, doxorubicin HCl, droperidol, fentanyl citrate, heparin sodium, hydrocortisone sodium phosphate, hydroxyzine HCl, insulin (regular), lidocaine HCl, magnesium sulfate, mannitol, meperidine HCl, methylprednisolone sodium succinate, morphine sulfate, multivitamin infusion (MVI), pentazocine lactate, potassium acetate/chloride/phosphate, prochlorperazine edisylate, TPN solution (25% dextrose with 4.25% *Travasol*® with or without electrolytes), verapamil, and vitamin B-complex with vitamin C.

Metoclopramide is reported to be physically **incompatible** when mixed with the following drugs: ampicillin sodium, calcium gluconate, cephalothin sodium, chloramphenicol sodium succinate, cisplatin, erythromycin lactobionate, methotrexate sodium, penicillin G potassium, sodium bicarbonate, and tetracycline. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

All doses expressed in terms of metoclopramide monohydrate.

Metoclopramide HCl Tablets: 5 mg & 10 mg; *Maxolon*® (SK-Beecham); *Reglan*® (Schwarz Pharma); generic; (Rx)

Metoclopramide HCl Syrup: 1 mg/mL in 480 mL and UD 10 mL; generic; (Rx) Metoclopramide HCl Injection: 5 mg/mL in 2mL, 10 mL, 20mL, 30 mL vials, & 2 mL amps, and preservative free in 2 mL, 10 mL, 30 mL vials; and 2 mL and 10 mL amps; *Reglan*® (Wyeth-Ayerst); *Octamide PFS*® (Adria); generic; (Rx)

METOPROLOL TARTRATE
METOPROLOL SUCCINATE

(me-***toe***-pro-lole) Lopressor®, Toprol XL®

BETA-ADRENERGIC BLOCKER

Prescriber Highlights

- Beta$_1$-blocker used for supraventricular tachyarrhythmias, premature ventricular contractions (PVC's, VPC's), systemic hypertension, & treatment in cats with hypertrophic cardiomyopathy
- Probably safer to use than propranolol in animals with bronchoconstrictive disease
- Contraindications: Overt heart failure, hypersensitivity beta-blockers, greater than first-degree heart block, or sinus bradycardia
- Caution: Significant hepatic insufficiency, bronchospastic lung disease, CHF, hyperthyroidism (masks clinical signs, but may be useful for treatment), labile diabetics, & sinus node dysfunction
- Adverse Effects: Most common in geriatric animals or those that have acute decompensating heart disease, include: bradycardia, lethargy & depression, impaired AV conduction, CHF or worsening of heart failure, hypotension, hypoglycemia, bronchoconstriction, syncope, & diarrhea
- Try to wean off drug gradually

Uses/Indications

Because metoprolol is relatively safe to use in animals with bronchospastic disease, it is often chosen over propranolol. It may be effective in supraventricular tachyarrhythmias, premature ventricular contractions (PVC's, VPC's), systemic hypertension, and treating cats with hypertrophic cardiomyopathy. There is increasing interest in using beta blockers in heart failure in dogs; one retrospective study showed increased survival times when dogs were given metoprolol, but definitive prospective, double-blinded studies have not been reported documenting the benefit (increased survival) of beta-blockers in dogs with heart failure.

Pharmacology/Actions

Metoprolol is a relatively specific beta$_1$-blocker and is sometimes characterized as a second generation beta blocker. At higher dosages, this specificity may be lost and beta$_2$ blockade can occur. Metoprolol does not possess any intrinsic sympathomimetic activity like pindolol nor does it possess membrane-stabilizing activity like pindolol or propranolol. Cardiovascular effects secondary to metoprolol's negative inotropic and chronotropic actions include: decreased sinus heart rate, slowed AV conduction, diminished cardiac output at rest and during exercise, decreased myocardial oxygen demand, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia.

Pharmacokinetics

Metoprolol tartrate is rapidly and nearly completely absorbed from the GI tract, but it has a relatively high first pass effect (50%) so systemic bioavailability is reduced. The drug has very low protein binding characteristics (5–15%) and is distributed well into most tissues. Metoprolol crosses the blood-brain barrier and CSF levels