METHADONE HCL

(***meth***-a-done) Dolophine®

OPIATE AGONIST

Prescriber Highlights

- Narcotic agonist that may be used as an alternative to morphine in dogs, cats
- Causes less histamine-release (with IV), sedation & vomiting than morphine
- Depending on country, may be significantly more expensive than morphine
- C-II controlled substance in USA

Uses/Indications

Methadone may be used as an alternative opioid preanesthetic or analgesic in dogs or cats. It is also being investigated for epidural use for horses.

Pharmacology/Actions

In small animals methadone acts similarly to morphine with regard to its degree of analgesia and duration of action. Methadone is a *mu*-receptor agonist that also is a non-competitive inhibitor of NMDA (n-methyl-d-aspartate) receptors. Methadone is more lipid-soluble than is morphine and approximately 1–1.5 times as potent. It does not cause significant histamine release when administered intravenously.

Refer to the monograph: *Narcotic (opiate) Analgesic Agonists, Pharmacology of,* for more information.

Pharmacokinetics

Limited information is available on the pharmacokinetics of methadone in domestic animals. One study in dogs showed a terminal elimination half-life of 2–3 hours. In humans, methadone is well absorbed from the GI tract (PO), and after subcutaneous or intramuscular injection. It is widely distributed and extensively bound to plasma proteins (60–90%). Methadone is metabolized in the liver primarily by the cytochrome P450 CYP3A isoenzyme, but other isoenzymes also play a role. Metabolites do not have activity. Methadone half-life is widely variable in humans (15–60 hours); elimination half-lives may be extended if giving multiple doses.

Contraindications/Precautions/Warnings

All opiates should be used with caution in patients with head injuries, elevated CSF pressures, and in geriatric or severely debilitated patients.

Adverse Effects

Adverse effects from methadone can include sedation, vomiting, defecation, constipation, bradycardia, and respiratory depression. Methadone tends to cause less sedation or vomiting than morphine.

Reproductive/Nursing Safety

Methadone is relatively safe to use at low dosages for short periods during the first two trimesters of pregnancy, but it should be avoided late in term as significant respiratory depression and increased rates of stillbirths have been noted in humans. Infants of humans who have been taking methadone for opiate addiction, have shown high rates of moderate to severe opiate withdrawal signs during the neonatal period, and long-term developmental problems.

Although methadone enters maternal milk, the American Academy of Pediatrics considers methadone compatible with breast-feeding in women.

Overdosage/Acute Toxicity

Overdosage may produce profound respiratory and/or CNS depression in most species. Newborns may be more susceptible to these effects than adult animals. Other toxic effects can include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated. Animals should be closely observed since naloxone's effects might diminish before sub-toxic levels of methadone are attained. Mechanical respiratory support should be considered in cases of severe respiratory depression. Dialysis, charcoal hemoperfusion, or forced diuresis do not appear to be beneficial in treating methadone overdoses.

Drug Interactions

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

- **ANTIARRHYTHMICS, CLASS I & III** (*e.g.*, **lidocaine, procainamide, quinidine, amiodarone**): Use with methadone may increase risks for arrhythmias
- **AZOLE ANTIFUNGALS** (**fluconazole, itraconazole, ketoconazole**): May increase methadone levels
- **CALCIUM CHANNEL BLOCKERS**: Use with methadone may increase risks for arrhythmias
- **CNS DEPRESSANTS, OTHER** (*e.g.*, **anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol,** etc.): May cause increased CNS or respiratory depression when used with methadone
- **CORTICOSTEROIDS** (**MINERALOCORTICOIDS**): Use with methadone may increase potential for electrolyte abnormalities
- **DIURETICS**: Opiates may decrease efficacy in CHF patients
- **MACROLIDE ANTIBIOTICS** (**erythromycin, clarithromycin**): May inhibit metabolism of methadone and increase levels
- **MONAMINE OXIDASE** (**MAO**) **INHIBITORS** (*e.g.*, **amitraz**, possibly **selegiline**): Meperidine with MAOIs in humans has caused severe CNS/behavior reactions and potentially could do the same with methadone; avoid concomitant use
- **MUSCLE RELAXANTS, SKELETAL**: Methadone may enhance neuromuscular blockade
- **PHENOBARBITAL, PHENYTOIN**: May decrease methadone levels
- **RIFAMPIN**: May decrease methadone levels
- **SSRI ANTIDEPRESSANTS** (**fluoxetine, sertraline,** etc.): May increase methadone levels
- **St JOHN'S WORT**: May decrease methadone levels
- **TRICYCLIC ANTIDEPRESSANTS** (**clomipramine, amitriptyline,** etc.): Methadone may exacerbate the effects of tricyclic antidepressants
- **WARFARIN**: Opiates may potentiate anticoagulant activity
- **ZIDOVUDINE**: Methadone may increase zidovudine levels

Laboratory Considerations

- As they may increase biliary tract pressure, opiates can increase plasma **amylase** and **lipase** values up to 24 hours following their administration.

Doses

■ **DOGS:**

a) As a pre-anesthetic: 0.2–0.5 mg/kg SC, IM; or a combination of methadone 0.1–0.3 mg/kg with acepromazine 0.02–0.05 mg/kg SC, IM (Cornell 2004)

b) For pain: 0.1–0.25 mg/kg IM, SC, IV. Duration of effect 4–6 hours. (Otero 2006a)

c) For perioperative pain control: 0.1–0.5 mg/kg IM or SQ; duration of effect is 2–4 hours. (Pascoe 2006)

■ **CATS:**

a) For perioperative pain control: 0.05–0.5 mg/kg IV, IM or SC q4–6h (Tranquilli 2003)

b) As a pre-anesthetic: 0.1–0.2 mg/kg SC, IM; or a combination of methadone 0.1–0.3 mg/kg with acepromazine 0.02–0.05 mg/kg SC, IM (Cornell 2004)

c) For moderate to severe pain: 0.1–0.2+ mg/kg IM or SQ; duration of effect is 2–6 hours. For IV dosing use ½ the low end dose, titrate over 3–5 minutes; duration of effect is 1–4 hours. (Mathews 2006)

d) For pain: 0.1–0.2 mg/kg SC, IV. Duration of effect 2–3 hours. (Otero 2006a)

Monitoring

■ Analgesic or preanesthetic efficacy

■ At higher dosages, monitor for respiratory depression

Client Information

■ When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.

■ If being used orally for pain control, be sure to keep out of reach of children and pets.

Chemistry/Synonyms

A synthetic diphenylheptane-derivative narcotic agonist, methadone HCl occurs as an odorless, colorless or white crystalline powder. It is freely soluble in water, chloroform, or alcohol and practically insoluble in ether or glycerol. The pH of a 1% solution in water is between 4.5 and 6.5. The commercially available injection has a pH from 3–6.5. The dispersible tablet formulation (*Diskets®*) contains insoluble ingredients that deter their use for injection.

Methadone may also be known as: Amidine HCl, amidone HCl, methadoni hydrochloridum, Phenadone, *Adolan®, Biodone®, Cloro Nona®, Dolmed®, Eptadone®, Gobbidona®, Heptadon®, Ketalgine®, Metadol®, Metasedin®, Methaddict®, Methadose®, Methatabs®, Methex®, Pallidone®, Phymet®, Physeptone®, Pinadone®, Sedo®, Symoron®,* or *Synastone®*.

Storage/Stability/Compatibility

Unless otherwise labeled, methadone products should be stored at room temperature and protected from light.

Methadone injection is reportedly stable when mixed in a syringe with acepromazine. The injection is reportedly **not compatible** with pentobarbital, phenobarbital, amobarbital, or thiopental.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 1 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Methadone HCl Injection: 10 mg/mL in 20 mL multidose vials; Methadone Hydrochloride (aaiPharma); (Rx, C-II)

Methadone HCl Tablets: 5 mg & 10 mg; Dispersible Tablets 40 mg; *Dolophine® Hydrochloride* (Roxane); *Methadose®* (Mallinckrodt); generic; (Rx, C-II)

Methadone HCl Oral Solution/Concentrate: 1 mg/mL, & 10 mg/mL (also in sugar & dye free) in 30 mL, 500 mL, 946 mL & 1 L; Methadone Hydrochloride (Roxane); *Methadose® (Mallinckrodt);* (Rx, C-II)

All methadone-containing products are C-II controlled substances in the USA. When used as an analgesic, methadone may be dispensed by any pharmacy or practitioner registered with the DEA for Class-II narcotics. When methadone is used to treat narcotic addiction, specialized approval must be obtained from the FDA and, usually, state regulators.

METHAZOLAMIDE

(meth-a-***zoe***-la-mide) Neptazane®

CARBONIC ANHYDRASE INHIBITOR

Prescriber Highlights

- Oral carbonic anhydrase inhibitor used primarily for open angle glaucoma
- Contraindicated in patients with significant hepatic, renal, pulmonary or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis or electrolyte imbalance
- Give oral doses with food if GI upset occurs
- Monitor with tonometry for glaucoma; check electrolytes

Uses/Indications

Orally administered methazolamide is used for the medical treatment of glaucoma.

Pharmacology/Actions

The carbonic anhydrase inhibitors act by a noncompetitive, reversible inhibition of the enzyme carbonic anhydrase. This reduces the formation of hydrogen and bicarbonate ions from carbon dioxide and reduces the availability of these ions for active transport into body secretions.

Pharmacologic effects of the carbonic anhydrase inhibitors include decreased formation of aqueous humor, thereby reducing intraocular pressure; increased renal tubular secretion of sodium and potassium and, to a greater extent, bicarbonate, leading to increased urine alkalinity and volume; anticonvulsant activity, which is independent of its diuretic effects (mechanism not fully understood, but may be due to carbonic anhydrase or a metabolic acidosis effect).

Pharmacokinetics

Little information is available. Methazolamide is absorbed from the GI tract albeit more slowly than acetazolamide. It is distributed throughout the body, including the CSF and aqueous humor. Methazolamide is at least partially metabolized in the liver.

Contraindications/Precautions/Warnings

Carbonic anhydrase inhibitors are contraindicated in patients with significant hepatic disease (may precipitate hepatic coma), renal or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis or electrolyte imbalance. They should not be used in patients with severe pulmonary obstruction unable to increase alveolar ventilation or those who are hypersensitive to them.