While methoxyflurane, potentially, may cause hepatotoxicity, this apparently occurs rarely and may be associated with hypoxic episodes. Nevertheless, it should be used with caution in patients with preexisting hepatic dysfunction.

Reproductive/Nursing Safety
Studies are not definitive, but methoxyflurane may cause teratogenic effects; other inhalant anesthetic agents may be safer alternatives. If methoxyflurane is used during delivery or C-section, oxygen may need to be given to newborns after delivery. In a system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Overdosage/Acute Toxicity
Overdosage or acute toxicities may cause circulatory depression and hypotension, cardiac arrhythmias, bradycardia, prolonged respiratory depression, emergence delirium, or malignant hyperthermic crises.

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

- **CLINDAMYCIN, LINCOMYCIN:** Should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur
- **NEPHROTOXIC DRUGS, OTHER** (*e.g.*, **aminoglycosides, amphotericin B, cisplatin, NSAIDs, penicillamine**): Because of methoxyflurane's potential for causing nephrotoxicity, it should not be used concurrently with other nephrotoxic drugs
- **NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS:** Should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur
- **SUCCINYLCHOLINE:** Concomitant administration of succinylcholine with inhalation anesthetics may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and, in susceptible patients, malignant hyperthermia as well
- **SYMPATHOMIMETICS** (**dopamine, epinephrine, norepinephrine, ephedrine, metaraminol**, etc.): While methoxyflurane sensitizes the myocardium to the effects of sympathomimetics less so than halothane, arrhythmias may still result; caution and monitoring are advised

Doses
- **DOGS & CATS:**
  a) 3% (induction); 0.5–1.5% (maintenance) (Papich 1992)
- **RUMINANTS & SWINE:**
  a) Induction 1%; maintenance 0.5% (Howard 1993)

Monitoring
- Respiratory and ventilatory status
- Cardiac rate/rhythm; blood pressure (particularly with "at risk" patients
- Level of anesthesia
- Renal function tests, if patient's post-operative urine output is excessive or markedly reduced

Chemistry/Synonyms
An inhalant general anesthetic agent, methoxyflurane occurs as a clear, mobile liquid. It has a characteristic fruity odor. Methoxyflurane is very slightly soluble in water and miscible with alcohol or olive oil. At 20°C, methoxyflurane's specific gravity is 1.420–1.425.

Methoxyflurane may also be known as NSC-110432, *Penthrane*® and *Penthrox*®.

Storage/Stability/Compatibility
Store at room temperature in tight, light-resistant containers. Protect from freezing. Methoxyflurane is very soluble in rubber and soda lime. Avoid contact with polyvinyl chloride (PVC) plastics as they can be extracted by methoxyflurane.

Methoxyflurane contains an antioxidant (BHT) that may accumulate in the vaporizer causing a yellow to brown discoloration. Do not use discolored solutions. Discolored vaporizer and wick may be cleaned with diethyl ether (all ether must be removed before reuse).

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Methoxyflurane in 15 mL and 125 mL; *Penthrane*® (Abbott); (Rx)

METHYLENE BLUE

(***meth***-i-leen)

ANTIDOTE

Prescriber Highlights
- Thiazine dye used to primarily treat methemoglobinemia in ruminants
- Contraindications: Cats (most agree), lactating dairy animals, renal insufficiency; hypersensitive to methylene blue; or given as an intraspinal (intrathecal) injection
- Not very effective in horses
- Adverse Effects: Heinz body anemia or other red cell morphological changes, methemoglobinemia, & decreased red cell life spans. Cats most sensitive, but to a lesser degree, dogs & horses also.
- A 180-day slaughter withdrawal time has been suggested, but 14 days may be sufficient (see doses)

Uses/Indications
Methylene blue is used primarily for treating methemoglobinemia secondary to oxidative agents (nitrates, chlorates) in ruminants. It is also employed occasionally as adjunctive or alternative therapy for cyanide toxicity.

Intra-operative methylene blue is also being used to preferentially stain islet-cell tumors of the pancreas in dogs in order to aid in their surgical removal or in determining the animal's prognosis.

Pharmacology/Actions
Methylene blue is rapidly converted to leucomethylene blue in tissues. This compound serves as a reducing agent that helps to convert methemoglobin (Fe^{+++}) to hemoglobin (Fe^{++}). Methylene blue is an oxidating agent, and, if high doses (species dependent) are administered, may actually cause methemoglobinemia.

Pharmacokinetics
Methylene blue is absorbed from the GI tract, but is usually administered parenterally in veterinary medicine. It is excreted in the urine and bile, primarily in the colorless form, but some unchanged drug may be also excreted.

Contraindications/Precautions/Warnings
Methylene blue is contraindicated in patients with renal insufficiency, or are hypersensitive to methylene blue. It cannot be given as an intraspinal (intrathecal) injection. Because cats may develop Heinz body anemia and methemoglobinemia secondary to methylene blue, it is considered contraindicated in this species by most clinicians. Methylene blue is considered relatively ineffective in reducing methemoglobin in horses.

Adverse Effects
The greatest concern with methylene blue therapy is the development of Heinz body anemia or other red cell morphological changes, methemoglobinemia, and decreased red cell life spans. Cats tend to be very sensitive to these effects; the drug is usually considered contraindicated in them, but dogs and horses can also develop these effects at relatively low dosages.

When injected SC or if extravasation occurs during IV administration, necrotic abscesses may develop.

Reproductive/Nursing Safety
Safe use of this agent during pregnancy has not been demonstrated. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

No information on lactation safety was found.

Overdosage/Acute Toxicity
The LD_{50} for IV administered 3% methylene blue is approximately 43 mg/kg in sheep.

Drug Interactions
None reported

Laboratory Considerations
- Methylene blue can cause a green-blue color in urine and may affect the accuracy of **urinalysis**.

Doses
- **DOGS:**

To preferentially stain islet-cell tumors of the pancreas:

a) 3 mg/kg in 250 mL sterile normal saline and administered IV over 30–40 minutes intraoperatively. Initial tumor staining requires approximately 20 minutes after infusion has begun and is maximal at about 25–35 minutes after infusion is started. Tumors generally appear to be a reddish-violet in color versus a dusky blue (background staining). (Fingeroth and Smeak 1988)

To treat methemoglobinemia:

a) Secondary to phenol exposure: A single, slow IV infusion of 4 mg/kg of methylene blue; may use with 20 mg/kg ascorbic acid PO (Dorman and Clark 2000)

b) For severe methemoglobinemia: 1 mg/kg as a 1% solution given slowly IV over several minutes. A dramatic response should occur during the first 30 minutes after treatment. It may be repeated if necessary, but it should be used cautiously as can cause Heinz body anemia. Measure hematocrit for 3 days after treatment. (Harvey 2006)

- **CATS:**

To treat methemoglobinemia:

a) Secondary to phenol exposure: A single, slow IV infusion of 1.5 mg/kg of methylene blue, may use with 20 mg/kg ascorbic acid PO (Dorman and Clark 2000)

b) 1–1.5 mg/kg IV one time only (Christopher 2000)

c) For severe methemoglobinemia: 1 mg/kg as a 1% solution given slowly IV over several minutes. A dramatic response should occur during the first 30 minutes after treatment. It may be repeated if necessary, but it should be used cautiously as can cause Heinz body anemia. Measure hematocrit for 3 days after treatment. (Harvey 2006)

- **RUMINANTS:**

Note: When used in food animals, FARAD recommends a minimum milk withdrawal time of 4 days after the last treatment. Because of concerns of carcinogenicity, an extremely conservative withdrawal time for meat of 180 days has been recommended; however, available data suggest that a much shorter withdrawal time of 14 days would be sufficient. (Haskell, Payne et al. 2005)

For methemoglobin-producing toxins (nitrites, nitrates, chlorates):

a) Cattle: 8.8 mg/kg by slow IV using a maximum of a 1% solution; repeat if necessary. To prevent hypotension during nitrite poisoning, give a sympathomimetic drug such as epinephrine or ephedrine. (Bailey 1986b)

b) Food animals: 4–15 mg/kg IV; may be repeated in 6–8 hours (Post and Keller 2000)

c) Cattle, sheep: 8.8 mg/kg slow IV as a 1% solution in normal saline; may repeat carefully in 15–30 minutes if response is not satisfactory. Other species should use 4.4 mg/kg dosage rate (as above). (Hatch 1988b)

d) For nitrate poisoning in cattle: 5–15 mg/kg as a 1% solution in physiologic saline. With severe cases, repeat treatment at a lower dose may be required. In animals that do not succumb, recovery occurs by 24 hours. (Hall 2006)

For cyanide toxicity:

a) 4–6 g IV per 454 kg (1000 lb.) of body weight (Oehme 1986b)

- **HORSES:**

For methemoglobinemia secondary to chlorate toxicity:

a) 4.4 mg/kg as 1% solution by intravenous drip; may repeat in 15–30 minutes if clinical response is not obtained. (Schmitz 2004)

Monitoring
- Methemoglobinemia
- Red cell morphology, red cell indices, hematocrit, hemoglobin

Client Information
- Because of the potential toxicity of this agent and the seriousness of methemoglobin-related intoxications, this drug should be used with close professional supervision only.
- Methylene blue may be very staining to clothing or skin. Removal may be accomplished using hypochlorite solutions (bleach).

Chemistry/Synonyms
A thiazine dye, methylene blue occurs as dark green crystals or crystalline powder that has a bronze-like luster. It may have a slight odor and is soluble in water and sparingly soluble in alcohol. When dissolved, a dark blue solution results. Commercially available methylene blue injection (human-labeled) has a pH from 3–4.5.

Methylene blue may also be known as: methylthioninium chloride, azul de metileno, blu di metilene, CI basic blue 9, colour index no. 52015, methylene blue, methylenii caeruleum, methylthioninii chloridum, schultz no. 1038, tetramethylthionine chloride trihydrate, *Azul Metile®, Collubleu®, Desmoidpillen®, Vitableu®, Urolene Blue®* and *Zumetil®*.

Storage/Stability/Compatibility

Unless otherwise instructed by the manufacturer, store methylene blue at room temperature. Methylene blue is reportedly physically **incompatible** when mixed with caustic alkalies, dichromates, iodides, and oxidizing or reducing agents.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

None approved as pharmaceuticals for internal use. A 1% (10 mg/mL) methylene blue solution (Centaur) is labeled for animal use as a dye, laboratory indicator and reagent. It is available in pint and gallon bottles. Methylene Blue, USP powder may be available from chemical supply houses

HUMAN-LABELED PRODUCTS:

Methylene Blue Injection: 10 mg/mL in 1 mL and 10 mL amps; generic; (Rx)

Methylene Blue Tablets: 65 mg; *Urolene Blue®* (Star); (Rx)

METHYLPHENIDATE

(meth-ill-***fen***-i-date) Ritalin®

CNS STIMULANT

Prescriber Highlights

- Amphetamine-like drug that may be useful for treating cataplexy/narcolepsy or hyperkinesis/hyperactivity in dogs
- Use with caution in dogs with seizure disorders, cardiac disease/hypertension, or in aggressive animals
- Adverse effects are primarily CNS stimulation-related
- Class-II controlled drug in USA

Uses/Indications

Methylphenidate may be useful for treating cataplexy/narcolepsy or hyperactivity in dogs.

Pharmacology/Actions

Methylphenidate has stimulating effects on the central nervous and respiratory systems similar to that of amphetamines. It also has weak sympathomimetic activity, and at normal dosages has little effect on peripheral circulation.

Pharmacokinetics

Specific pharmacokinetic studies in dogs were not located. In humans, methylphenidate (regular tablets) is rapidly and well absorbed from the GI tract. Food in the GI tract may increase the rate, but not the extent, of drug absorbed. Peak levels occur about 2 hours post-dose. The drug is extensively metabolized during the first-pass; protein binding is low. Terminal elimination half-life is approximately 3 hours; less than 1% is excreted unchanged in the urine.

Contraindications/Precautions/Warnings

The risks associated with methylphenidate should be carefully considered before using this drug in dogs with seizure disorders, cardiac disease/hypertension, or in aggressive animals.

Adverse Effects

Most likely adverse effects to be encountered include increased heart and respiratory rates, anorexia, tremors and hyperthermia (particularly exercised-induced).

Reproductive/Nursing Safety

In humans, the FDA categorizes methylphenidate as a category ***C*** drug for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans*). Methylphenidate was associated with teratogenic effects in rabbits, but at massive dosages (200 mg/kg/day).

It is unknown if methylphenidate enters maternal milk.

Overdosage/Acute Toxicity

In dogs, dosages of 1 mg/kg (or below) can cause toxic reactions; there is one report of a fatality after a dog ingested 3.1 mg/kg, but research dogs have survived doses of 20 mg/kg/day for 90 days. A cat given a 5 mg tablet of methylphenidate, showed signs of tremors, agitation, mydriasis, tachycardia, tachypnea and hypertension; signs resolved 25 hours post-ingestion with supportive care (dark cage, diazepam, fluids).

Expected signs associated with an overdose in dogs are generally CNS over-stimulation and excessive sympathomimetic effects and can include: hyperactivity, salivation, diarrhea, head bobbing, agitation, tachycardia, hypertension, tremors, seizures, and hyperthermia. Consider the dosage form (extended-release vs. regular tablets) when considering treatment options and expected onset and duration of effects. Employ treatment using standard gut detoxification techniques (emetic, activated charcoal, cathartic, etc.); however, emesis should be avoided in animals displaying signs associated with toxicity or that are otherwise at risk for emesis-related adverse effects. Treatment is basically supportive by controlling signs associated with toxicity. Phenothiazines (*e.g.*, acepromazine, chlorpromazine) may be useful in controlling agitation; beta-blockers can help control tachycardia; external cooling may be used for hyperthermia; and cyproheptadine may help prevent serotonin syndrome.

Drug Interactions

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

- **ANTICONVULSANTS** (**phenobarbital, primidone, phenytoin**): Methylphenidate may increase serum levels
- **CLONIDINE:** Rare cases (in humans) of cardiovascular effects (including death); mechanism not understood and causality not established
- **HYPOTENSIVE DRUGS:** Methylphenidate may reduce effects
- **MAO INHIBITORS** (including **amitraz** and potentially, **selegiline**): Could lead to hypertensive crisis
- **SSRI ANTIDEPRESSANTS** (*e.g.*, **fluoxetine**, **sertraline**, etc.): Methylphenidate may inhibit metabolism and increase levels
- **TRICYCLIC ANTIDEPRESSANTS** (*e.g.*, **amitriptyline**, **clomipramine**, etc.): Methylphenidate may inhibit metabolism and increase levels
- **WARFARIN:** Methylphenidate may inhibit warfarin metabolism and increase INR