Metronidazole

- (me-troe-**ni-**da-zole)
- *Flagyl*®
- Antibiotic, Antiparasitic

PRESCRIBER HIGHLIGHTS

- Injectable & oral antibacterial (anaerobes) & antiprotozoal agent.
- Prohibited by the FDA for use in food animals.
- Contraindications: Hypersensitivity to it or other nitroimidazole derivatives. Extreme caution: in severely debilitated, pregnant or nursing animals; hepatic dysfunction. May be a teratogen, especially in early pregnancy.
- Adverse Effects: Neurologic disorders, lethargy, weakness, neutropenia, hepatotoxicity, hematuria, anorexia, nausea, vomiting, & diarrhea.
- Very bitter, metronidazole benzoate may be more palatable when compounded.

USES/INDICATIONS

Although there are no veterinary-approved metronidazole products, the drug has been used extensively in the treatment of Giardia in both dogs and cats. It is also used clinically in small animals for the treatment of other parasites (Trichomonas and *Balantidium coli*) as well as treating both enteric and systemic anaerobic infections. It is commonly employed as a perioperative surgical prophylaxis antibiotic where anaerobes are likely (*e.g.*, colon; periodontal).

In horses, metronidazole has been used clinically for the treatment of anaerobic infections.

PHARMACOLOGY/ACTIONS

Metronidazole is a concentration-dependent bactericidal agent against susceptible bacteria. Its exact mechanism of action is not completely understood, but it is taken-up by anaerobic organisms where it is reduced to an unidentified polar compound. It is believed that this compound is responsible for the drug's antimicrobial activity by disrupting DNA and nucleic acid synthesis in the bacteria. Metronidazole has activity against most obligate anaerobes including *Bacteroides* spp. (including *B. fragilis*), Fusobacterium, Veillonella, *Clostridium* spp., Peptococcus, and Peptostreptococcus. Actinomyces is frequently resistant to metronidazole. Some isolates of *C. difficile* may be resistant.

Metronidazole is also trichomonacidal and amebicidal in action and acts as a direct amebicide. Its mechanism of action for its antiprotozoal activity is not understood. It has therapeutic activity against *Entamoeba histolytica*, Trichomonas, Giardia, and *Balantidium coli*. It acts primarily against the trophozoite forms of Entamoeba rather than encysted forms.

Metronidazole has some inhibitive actions on cell-mediated immunity that may play a role in its use for treating inflammatory bowel disease.

PHARMACOKINETICS

Metronidazole is relatively well absorbed after oral administration. Metronidazole is rather lipophilic and is rapidly and widely distributed after absorption. It is distributed to most body tissues and fluids, including bone, abscesses, the CNS, and seminal fluid. Metronidazole is <20% bound to plasma proteins in humans. Metronidazole is primarily metabolized in the liver via several pathways. Both the metabolites and unchanged drug are eliminated in the urine and feces.

The oral bioavailability in dogs is high, but interpatient variable, with ranges from 50-100% reported. If given with food, absorption is enhanced in dogs, but delayed in humans. Peak levels occur ≈1 hour after oral dosing.

In a single-dose study in cats (Sekis *et al.* 2009), the oral bioavailability of metronidazole benzoate is variable, but averages around 65%. Peak levels after oral dosing appear to be highly variable in cats (ranging from 1-8 hours) and peak serum concentrations are somewhat lower in cats than in dogs or humans. Mean systemic clearance is slower in cats than dogs (2.49 mL/kg/min vs. 1.53 mL/kg/min). Despite the concern that glucuronidation is a metabolic pathway for metronidazole, terminal elimination half-life is only slightly (not significantly) longer (5-6 hours) in cats.

The oral bioavailability of the drug in horses averages ≈80% (range 57-100%). In adult horses, food does not appreciably alter oral absorption (Britzi *et al.* 2010). If administered rectally to horses, bioavailability is decreased by ≈50%. Elimination half-life in the horse is ≈2.9-4.3 hours.

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS

Metronidazole is prohibited for use in food animals by the FDA.

Metronidazole is contraindicated in animals hypersensitive to the drug or nitroimidazole derivatives. It has been recommended not to use the drug in severely debilitated, pregnant or nursing animals. Metronidazole should be used with caution in animals with hepatic dysfunction. If the drug must be used in animals with significant liver impairment, consider reducing the total daily dose to 1/3 of standard anti-anaerobe dosage and dose once daily (Trepanier 2013).

Because of the risk for neurotoxicity in dogs, total daily doses of metronidazole should not exceed 65 mg/kg per day (Tams 2007).

ADVERSE EFFECTS

Adverse effects reported in dogs include neurologic disorders, lethargy, weakness, neutropenia, hepatotoxicity, hematuria, anorexia, nausea, vomiting, and diarrhea. Rare cases of cutaneous vasculitis associated with metronidazole have been reported. Neurologic toxicity in dogs may occur after acute high dosages or more likely, with chronic moderate to high-dose therapy. Clinical signs reported are described below in the Overdosage section.

In cats, vomiting, inappetence, hepatotoxicity and rarely, central nervous toxicity can occur with metronidazole therapy (Scorza *et al.* 2004). Genotoxicity was detected in peripheral blood mononuclear cells collected from cats after 7 days of oral metronidazole, but resolved within 6 days of discontinuing the drug. Clinical significance, particularly with chronic therapy, is yet to be determined (Sekis *et al.* 2009).

In horses, metronidazole may occasionally cause anorexia, ataxia and depression, particularly when used at higher dosages. There have been reported cases of *C. difficile* and *C. perfringens* diarrhea and death after use of metronidazole.

Metronidazole tablets have a sharp, metallic taste that animals find unpleasant. Placing in capsules or using compounded oral suspensions may alleviate the problem of dosing avoidance.

REPRODUCTIVE/NURSING SAFETY

Metronidazole's potential for teratogenicity is somewhat controversial; some references state that it has been teratogenic in some laboratory animal studies, but others state that it has not. However, unless the benefits to the mother outweigh the risks to the fetus(es), it should not be used during pregnancy, particularly during the first 3 weeks of gestation. 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: ***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*.)

Because of the potential for tumorigenicity, consider using alternative therapy or switching to milk replacer for nursing patients.

OVERDOSAGE/ACUTE TOXICITY

Signs of intoxication associated with metronidazole in dogs and cats, include anorexia and/or vomiting, depression, mydriasis, nystagmus, ataxia, head-tilt, deficits of proprioception, joint knuckling, disorientation, tremors, seizures, bradycardia, rigidity and stiffness. These effects may be seen with acute overdoses, doses in dogs above 60 mg/kg per day, or in some animals on chronic therapy when using older "recommended" doses (*e.g.,* 30 mg/kg/day).

In dogs, common signs of metronidazole toxicity include generalized ataxia with a very rapid positional nystagmus. Most often, dogs have neurological deficits localized to the central vestibular system and/or cerebellum. Dogs with mild to moderate clinical signs usually improve rapidly within 1-2 days, once metronidazole has been discontinued (Vernau 2009).

Diazepam has been used successfully to decrease the CNS effects associated with metronidazole toxicity, but has not been evaluated in a controlled manner. See the Diazepam monograph or the reference by Evans, Levesque, et al for more information (Evans *et al.* 2002).

Acute overdoses should be handled by attempting to limit the absorption of the drug using standard protocols. Extreme caution should be used before attempting to induce vomiting in patients demonstrating CNS effects or aspiration may result. If acute toxicity is seen after chronic therapy, the drug should be discontinued and the patient treated supportively and symptomatically. Neurologic clinical signs may require several days before showing signs of resolving.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving metronidazole and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Alcohol**: May induce a disulfiram-like (nausea, vomiting, cramps, etc.) reaction when given with metronidazole.
- **Busulfan**: May result in increased busulfan levels and toxicity.
- **Cimetidine**: May decrease the metabolism of metronidazole and increase the likelihood of dose-related side effects.
- **Cyclosporine**: Use with metronidazole may increase cyclosporine levels.
- **Fluorouracil (5-FU)**: May result in increased fluorouracil levels and toxicity.
- **Phenobarbital** or **phenytoin**: May increase the metabolism of metronidazole, thereby decreasing blood levels.
- **Warfarin**: Metronidazole may prolong the PT in patients receiving warfarin or other coumarin anticoagulants. Avoid concurrent use if possible; otherwise, intensify monitoring.

Laboratory Considerations

- Metronidazole can cause falsely decreased readings of **AST** (SGOT) and **ALT** (SGPT) when determined using methods measuring decreases in ultraviolet absorbance when NADH is reduced to NAD.

Doses

Note: Doses are for **metronidazole base** unless otherwise noted. If using **metronidazole benzoate** adjust dosages unless provided by pharmacy as "mg/mL of the base". 1 mg of metronidazole base = 1.6 mg of metronidazole benzoate.

Dogs:

- **For treatment of giardiasis** (extra-label): The Companion Animal Parasite Council (CAPC) recommends fenbendazole (50 mg/kg PO once daily for 5 days) as its first choice drug, but fenbendazole can be used in combination with metronidazole at 25 mg/kg PO twice daily for 5 days. This combination therapy may result in better resolution of clinical disease and cyst shedding. If treatment combined with bathing (see Control and Prevention) does not eliminate infection (as evidenced by testing feces for persistence of cysts), treatment with either fenbendazole alone or in combination with metronidazole may be extended for another 10 days. If other pets live with an infected dog or cat, all those of the same species may also be treated with a single course of anti-giardial therapy. Repeated courses of treatment are not indicated in dogs or cats without clinical signs. (CAPC 2014)
- **For other protozoal infections** (extra-label): *Entamoeba histolytica* or *Pentatrichomas hominis*: 25 mg/kg PO q12h for 8 days. (Lappin 2000)
- **For perioperative surgical prophylaxis (colorectal surgery);** (extra-label): There is no consensus for dosages in veterinary medicine, but consider metronidazole 15 mg/kg IV over 30-60 minutes and completed approximately 1 hour before surgery. Usually used in conjunction with cefazolin.
- **For anaerobic infections** (extra-label): **For sepsis**: 15 mg/kg IV q12h; for less severe anaerobic infections 10 – 15 mg/kg q8-12h can be considered.
- **For clostridial enteritis**: 10–15 mg/kg orally every 8-12 hours for 5 days. 15 mg/kg IV q12h for 5 days can be used if PO is not an option.
- **For adjunctive therapy of inflammatory GI conditions (IBD);** (extra-label): 10 – 15 mg/kg PO twice daily. Consider reducing dosage to 7.5 - 10 mg/kg PO twice daily in patients with concomitant hepatic disease. Long-term therapy has potential risks for neurotoxicosis and hepatotoxicosis.[x]
- **For treating Helicobacter gastritis infections** (extra-label): Using triple therapy: Metronidazole 15.4 mg/kg q8h, amoxicillin 11 mg/kg q8h and bismuth subsalicylate (original *Pepto-Bismol*®) 0.22 mL/kg PO q4-6h. Give each for 3 weeks. (Hall 2000)

Cats:

- **For treatment of giardiasis** (extra-label): The Companion Animal Parasite Council (CAPC) states: Data on treatment of cats with *Giardia* are lacking. However, cats may be treated with either fenbendazole at 50 mg/kg PO once daily for 5 days or metronidazole at 25 mg/kg PO twice daily for 5 days, or a combination of the two as described for dogs. There is anecdotal evidence that metronidazole benzoate is tolerated better in cats than

metronidazole (USP). If other pets live with an infected dog or cat, all those of the same species may also be treated with a single course of anti-giardial therapy. Repeated courses of treatment are not indicated in dogs or cats without clinical signs. (CAPC 2014)

- **For feline trichomoniasis** (*Tritrichomonas foetus*—most prevalent; *Pentatrichomonas hominis*); (extra-label): Metronidazole at 30 – 50 mg/kg PO twice daily for 3-14 days has been used in the past *for T. foetus*, but clearance of infections appears less common than when ronidazole is used. (CAPC 2014)
- **For perioperative surgical prophylaxis (colorectal surgery);** (extra-label): There is no consensus for dosages in veterinary medicine, but consider metronidazole 15 mg/kg IV over 30-60 minutes and completed approximately 1 hour before surgery. Usually used in conjunction with cefazolin.
- **For treating *H. pylori*** (extra-label): Metronidazole 10 – 15 mg/kg PO twice daily; clarithromycin 7.5 mg/kg PO twice daily; amoxicillin 20 mg/kg PO twice daily for 14 days. (Simpson 2003)
- **For anaerobic infections** (extra-label): For sepsis: 15 mg/kg IV q12h; for less severe anaerobic infections 10 – 15 mg/kg PO q12h or 15 – 25 mg/kg PO once daily can be considered. Practically, ¼ of a 250 mg (62.5 mg) per cat is often chosen for a PO dose; but because of the drug's extreme bitterness consider using compounded metronidazole benzoate or putting the quartered tablet in an empty gelatin capsule.
- **For clostridial enteritis**: 62.5 mg per cat PO q12h for 5 days.
- **For adjunctive therapy of inflammatory GI conditions (IBD);** extra-label): 10 – 15 mg/kg PO twice daily. Long-term therapy has potential risks for neurotoxicity and hepatotoxicity.

MONITORING

- Clinical efficacy.
- Adverse effects (clients should report any neurologic signs).

CLIENT INFORMATION

- Report any neurologic clinical signs to veterinarian (see Overdose section).

CHEMISTRY/SYNONYMS

A synthetic, nitroimidazole antibacterial and antiprotozoal agent, metronidazole occurs as white to pale yellow crystalline powder or crystals with a pK_a of 2.6. It is sparingly soluble in water or alcohol. Metronidazole base is commercially available as tablets or solution for IV injection and

metronidazole HCl is available as injectable powder for reconstitution. The hydrochloride is very soluble in water.

Metronidazole benzoate is the benzoic ester of metronidazole. It occurs as a white to slightly yellow, crystalline powder that is practically insoluble in water, slightly soluble in alcohol, and soluble in acetone. As it is less soluble in aqueous solutions than is the base, it does not taste as bad.

Metronidazole may also be known as: Bayer-5360, metronidazolum, SC-32642, NSC-50364, RP-8823, and SC-10295; many trade names are available.

STORAGE/STABILITY

Metronidazole tablets and HCl powder for injection should be stored at temperatures <30°C and protected from light. The injection should be protected from light and freezing and stored at room temperature.

Specific recommendations on the reconstitution, dilution, and neutralization of metronidazole HCl powder for injection are detailed in the package insert of the drug and should be referred to if this product is used. Do not use aluminum hub needles to reconstitute or transfer this drug as a reddish-brown discoloration may result in the solution.

COMPATIBILITY/COMPOUNDING CONSIDERATIONS

The following drugs and solutions are reportedly physically **compatible** with metronidazole ready-to-use solutions for injection: amikacin sulfate, aminophylline, cefazolin sodium, cefotaxime sodium, cefoxitin sodium, cefuroxime sodium, chloramphenicol sodium succinate, clindamycin phosphate, disopyramide phosphate, gentamicin sulfate, heparin sodium, hydrocortisone sodium succinate, hydromorphone HCl, magnesium sulfate, meperidine HCl, morphine sulfate, multielectrolyte concentrate, multivitamins, penicillin G sodium, and tobramycin sulfate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

The following drugs and solutions are reportedly physically **incompatible** (or compatibility data conflicts) with metronidazole ready-to-use solutions for injection: aztreonam, cefamandole naftate, and dopamine HCl.

Metronidazole hydrochloride is very bitter tasting and even with taste masking or flavoring agents is universally unpalatable to veterinary patients. Although not commercially available in the United States, the metronidazole ester of benzoic acid, metronidazole benzoate, is relatively palatable to animal patients and is often used in extemporaneously compounded suspensions, particularly for cats to reduce the drug's bitterness. If using metronidazole benzoate adjust dosages from those for the base unless provided by pharmacy as "mg/mL of the base". One mg of metronidazole base ≈ 1.6 mg of metronidazole benzoate. Crystallization and sedimentation can occur in aqueous

metronidazole benzoate suspensions when conversion from the anhydrous to the monohydrate form occurs.

Compounded preparation stability: One method for compounding a metronidazole benzoate suspension (80 mg/mL) that is stable (when protected from light, ambient temperature) for at least a year, has been published (Vu *et al.* 2008). To make 750 mL of an 80 mg/mL suspension: Place metronidazole benzoate powder 60 grams in a suitable mortar. The powder is then triturated with 1.25 grams of Propylene Glycol, NF to a smooth paste, then add increasing amounts of *SyrSpend SF* (Gallipot) until the suspension is pour-able. The liquid suspension should then be transferred to a suitable graduated container and the mortar rinsed with three small aliquots of *SyrSpend SF*, which are then added to the suspension. Add additional *SyrSpend SF* to bring the suspension to the final volume of 750 mL. Store in light-resistant containers refrigerated or at room temperature.

Another published method is to triturate 9.6 grams (9,600 mg) of metronidazole benzoate powder with 60 mL of *Ora-Plus*® and *qs ad* to 120 mL with *Ora-Sweet*® or *Ora-Sweet SF*® to yield a 80 mg/mL metronidazole benzoate oral suspension (equivalent to 50 mg/mL metronidazole hydrochloride) that retains >90% potency for 90 days when stored at both 4°C and 25°C and protected from light (Mathew *et al.* 1994).

DOSAGE FORMS/REGULATORY STATUS

Veterinary-Labeled Products: None.

Metronidazole is prohibited for use in food animals by the FDA.

Human-Labeled Products:

Metronidazole Oral Tablets: 250 mg & 500 mg; *Flagyl*®, generic; (Rx)

Metronidazole Oral Capsules: 375 mg; *Flagyl 375*®, generic; (Rx)

Metronidazole Extended-Release Oral Tablets: 750 mg; *Flagyl ER*®; (Rx)

Metronidazole Injection: 5 mg/mL in 100 mL vials and single-dose containers and 500 mg pre-mixed in sodium chloride for injection; (Rx)

Lotions, gels, vaginal products and creams also available.

REVISIONS/REFERENCES

Monograph revised/updated April 2014.

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