Feline Friendly Article

METHIMAZOLE
Management of Feline Hyperthyroidism

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Methimazole is commonly used for the pharmacologic management of feline hyperthyroidism.[1] This article reviews the properties of methimazole that are of importance to practitioners treating this common endocrinopathy.

PROFILE OF MEDICATION

Classification

This compound belongs to the imidazolethiones. These aromatic compounds contain an imidazole ring, which bears a thioketone group. Methimazole (1-methylimidazole-2-thiol; **Figure**) is a white, crystalline substance that is freely soluble in water. The chemical formula is $C_4H_6N_2S$; molecular weight is 114.16 daltons. Carbimazole, which is also used in the treatment of hyperthyroidism in cats, is a prodrug, which is converted to methimazole in the liver.

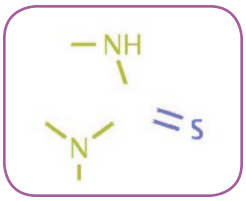

Figure. *Chemical structure for methimazole (1-methylimidazole-2-thiol).*

Mechanism of Action

Pharmacodynamics. Methimazole is a thioureylene antithyroid agent that inhibits formation of thyroid hormones by interfering with the incorporation of iodine into tyrosyl residues of thyroglobulin.

This process takes place by interfering with oxidation of iodide ion and iodotyrosyl groups through inhibition of the peroxidase enzyme. However, it does not affect the thyroid gland's ability to trap inorganic iodide or release preformed hormones (T3 and T4).

Methimazole has also been shown to inhibit vitamin K epoxide reductase, which can lead to bleeding disorders characterized by a prolonged PIVKA (proteins induced by vitamin K absence or antagonism) and, rarely, a prolonged prothrombin time.

Pharmacokinetics. Methimazole is minimally protein bound, metabolized in the liver, and excreted primarily in the urine. In cats, oral methimazole is rapidly absorbed, with:

- An oral bioavailability of 93%
- Maximal serum concentrations seen within 1.5 hours
- Mean half-life of 3.12 hours and serum concentrations at 24 hours—after a single oral 5-mg dose—of 21.7 ± 28.9 ng/mL.[2]

See **Transdermal Methimazole: How Does It Measure Up?** for more information on this route of administration and its mechanism of action.

APPLICATION IN VETERINARY MEDICINE

Indications

Methimazole is FDA-approved for the treatment of hyperthyroidism in cats. It may also be used to control hyperthyroidism in dogs with functional thyroid tumors (off-label use).

Methimazole (Felimazole, dechra-us.com) is approved for use in the U.S. and other countries, while carbimazole (Vidalta, merck-animal-health.com) is approved for use outside the U.S.

Contraindications

Methimazole should ***not*** be used in cats with:

1. Hypersensitivity to methimazole, carbimazole, or the excipient, polyethylene glycol
2. Coagulopathies or hematologic disorders, such as anemia, neutropenia, lymphopenia, or thrombocytopenia
3. Primary liver disease or renal failure (*or use cautiously*)
4. Pre-existing autoimmune disease because autoimmune disorders (see **Adverse Effects**, page 40) have been reported in cats taking methimazole.

Methimazole should also *not* be used in preg-

Transdermal Methimazole: How Does It Measure Up?

A recent pharmacokinetic study looked at a novel lipophilic formulation of methimazole—pluronic lecithin organogel (PLO)—for transdermal use and compared it with oral carbimazole.[3]

In the first 24 hours:

- Cats treated with **5 mg methimazole transdermally** did not have reliably detectable serum concentrations of methimazole
- Cats treated with **5 mg carbimazole orally** *or* **10 mg methimazole transdermally** had detectable serum concentrations of methimazole.

Compared with cats receiving **5 mg oral carbimazole**, those receiving **10 mg methimazole transdermally** had a:

- Lower maximum concentration and area under the curve
- Longer maximal concentration and elimination half-life
- Higher mean concentration in serum at 148 hours.

The mean relative bioavailability of 10 mg transdermal methimazole compared to oral carbimazole was 48% (min, 43%; max, 55%).

TABLE. COMPARISON OF TRANSDERMAL METHIMAZOLE & ORAL CARBIMAZOLE

MEDICATION	TIME AT MAX CONCENTRATION	ELIMINATION HALF-LIFE	MEAN CONCENTRATION (148 HOURS)
Carbimazole: 5 mg oral	2.1 (± 1.6) hours	5.1 (± 1.2) hours	255 (± 28) ng/mL
Methimazole: 5 mg transdermal	n/a	n/a	204 (± 76) ng/mL
Methimazole: 10 mg transdermal	5.2 (± 1.1) hours	13 (± 3) hours	506 (± 165) ng/mL

nant or lactating queens; laboratory studies in rats and mice have shown evidence of teratogenic and embryotoxic effects of this medication.

IN THE LITERATURE

A number of recent studies have evaluated the use of methimazole in cats with hyperthyroidism, evaluating its effects on renal and thyroid function, route of administration, and quality of life.

Best Use of Antithyroid Drugs

Hypertension, progression of chronic kidney disease, iatrogenic hypothyroidism, and persistence of hyperthyroidism are all concerns when managing patients with hyperthyroidism. A recent paper (2014) described the "best practice" of using antithyroid drugs for pharmacologic management of hyperthyroid cats.[4]

Treatment. Two drugs have been licensed for cats in the last decade: methimazole and its prodrug carbimazole. Based on current evidence and available tablet sizes, recommended starting doses include:

- **Methimazole: 2.5 mg PO Q 12 H**
- **Carbimazole** (sustained release formulation)**: 10 to 15 mg PO Q 24 H.**

These doses should then be titrated to effect in order to obtain circulating total thyroxine (TT4) concentrations in the lower half of the reference interval.

Monitoring. Patients should be monitored for side effects, especially during the first months of treatment. Some side effects may require discontinuation of treatment.

At each monitoring visit, clinical condition and quality of life should also be evaluated, with special attention to possible development of azotemia, hypertension, and iatrogenic hypothyroidism.

When euthyroidism has been achieved, monitoring visits are recommended after 1 month, 3 months, and twice yearly thereafter.

Survival Time. Cats with pre-existing azotemia have shorter survival times. However, development of mild azotemia during the initial course of treatment, unless associated with hypothyroidism, does not appear to decrease survival time.

Long-Term Effects. The long-term effects of chronic medical management require further study, including the value of monitoring free T4 (fT4) and thyroid stimulating hormone (TSH) concentration to detect subclinical hyper- and hypothyroidism, respectively.[4]

Owner Experiences with Management

A recent study (2013) surveyed 111 owners of hyperthyroid cats about their experiences and views on the management of hyperthyroidism.[5]

Treatment. The final treatment decision was usually based on the veterinarian's recommendation or joint decision-making between the owner and veterinarian.

- Oral antithyroid medication was offered to 92% of owners.
- Almost all cats (103/111; 93%) had received oral antithyroid medication at some point during the course of their disease.
- At survey completion, 69 cats (62%) were receiving oral antithyroid medication.

Results. Management of hyperthyroidism using United Kingdom veterinary-licensed oral antithyroid medication (methimazole or carbimazole) was associated with 72% to 75% success rates in terms of owner-assessed clinical outcome.

- The most important treatment priorities for owners were:
  - » Prescription of the most accurate dose of medication
  - » Use of lowest possible dose.
- No owners ranked once daily treatment as most important.
- Over three quarters (79%) of owners said that they were, or would be, happy to dose their cats twice daily to control hyperthyroidism.
- For 62% of owners, pilling their cats twice daily was not a problem.

Conclusion. These results suggest that, for most cat owners, there is no barrier to prescribing twice-daily antithyroid medication, if required.[5]

Transdermal Methimazole Treatment

A retrospective study (2013) was conducted to evaluate the efficacy and safety of long-term transdermal methimazole treatment in hyperthyroid cats. Sixty cats with newly diagnosed hyperthyroidism and available long-term follow-up information were included.[6]

Treatment & Monitoring. Methimazole was formulated in a PLO-based vehicle and applied to the pinna of the inner ear. Depending on clinician preference, the starting doses were:

- **2.5 to 5 mg/cat** administered in **1 dose (Q 24 H)** *or*
- **2.5 to 5 mg/cat** administered in **2 divided doses (Q 12 H)**.

Cats were re-evaluated at regular intervals, and median follow-up was 22.6 months.

Results. Clinical improvement was observed in all cats and side effects were rare (mild transient gastrointestinal signs, $n = 3$; erythema of the pinna, $n = 2$), but necessitated a switch to oral medication.

- Several cats repeatedly had T4 concentrations in the thyrotoxic and hypothyroid range, despite a significant decrease in overall median T4 concentrations into the reference interval during the follow-up period.
- After 24 to 36 months of therapy, maximal and minimal daily doses during the follow-up period were 15 and 1 mg, respectively, of which the former is significantly higher than the starting dose.
- Although the majority of owners were highly satisfied with treatment, several admitted not treating their cats regularly.

Conclusion. The authors concluded that transdermal methimazole is a safe option for the long-term management of feline hyperthyroidism. However, it seems difficult to maintain T4 concentrations consistently within the reference interval. A requirement for higher doses can be expected after prolonged treatment and, despite the convenience of transdermal application, owner compliance should be assessed regularly.[6]

ADMINISTRATION IN FELINE PATIENTS

Dosage

Starting doses for methimazole therapy have decreased since the disease was first discovered, mainly due to the lower concentrations of TT4 seen in the majority of hyperthyroid patients diagnosed today.

The suggested initial starting doses are:

- **Methimazole: 2.5 mg PO Q 12 H** or **2.5 mg transdermal Q 12 H**
- **Carbimazole** (sustained release): **10 to 15 mg PO Q 24 H**.

Route

Transdermal methimazole is suggested as an alternative to oral therapy for hyperthyroid cats that are difficult to pill. See **Transdermal Methimazole Treatment**, for further information on transdermal administration.

Duration

Methimazole can be used:

- **Short term** to control TT4 concentrations prior to more definitive therapy (radioactive iodine or surgery)
- **Long term** for medical management, with appropriate monitoring (see **MONITORING**, page 41).

Adverse Effects

Common. In cats, the most common side effects of methimazole/carbimazole administration are gastrointestinal (hyporexia to anorexia, vomiting, and diarrhea). Most of the gastrointestinal side effects can be controlled by discontinuation of the medication and supportive care. Once the signs have resolved, the medication can be restarted at a lower dose and titrated upward to achieve the desired clinical and biochemical endpoints.

Severe. More severe side effects include lymphadenopathy,[7] hepatopathies, aplastic anemia, thrombocytopenia, and agranulocytosis, which are generally manifested within the first few months of treatment.

Uncommon. Less frequent events include facial pruritus, exfoliative dermatitis, myasthenia gravis,[8] and a bleeding disorder secondary to vitamin K antagonism.

Drug Interactions

- **Anticoagulants** may be potentiated by the antivitamin K activity of methimazole.
- Decreased clinical efficacy of **phenobarbital** if the drugs are used concurrently.
- A reduction in dose of certain drugs (**alpha adrenergic blocking agents**, **digitalis glycosides**, and **theophylline**) may be needed when the patient becomes euthyroid.
- Methimazole is known to reduce the hepatic oxidation of benzimidazole anthelmintics (eg, **fenbendazole**), leading to increased plasma concentration of these anthelmintics when administered concurrently.

OWNER EDUCATION: 10 Key Points

Owners should be familiar with the following key points about methimazole.

Drug Facts

1. The veterinary approved formulations are not approved for use in humans.
2. Methimazole may cause vomiting, gastric distress, headache, fever, arthralgia, pruritus, and pancytopenia in humans.

Safe Use

3. The medication should be kept out of reach of children.
4. Tablets should not be broken or crushed.
5. Protective gloves should be worn to prevent direct contact with litter, feces, urine, or vomit of treated cats, and with broken or moistened tablets.
6. Owners should wash hands with soap and water after administration of the drug to avoid exposure.
7. Owners should also wash hands after handling the litter of treated cats.

Pregnancy & Lactation

8. Methimazole is a human teratogen and crosses the placenta, concentrating in the fetal thyroid gland. There is also a high rate of transfer into breast milk.
9. Pregnant women, women who may become pregnant, and nursing mothers should wear gloves when handling tablets, litter, or bodily fluids of treated cats.

Ingestion or Overdose

10. In the event of accidental ingestion/overdose, seek medical advice immediately, and show the product label to the physician.[10]

MONITORING

Follow-Up

At each monitoring visit, clinical signs and quality of life should be evaluated, with special attention to possible development of azotemia, hypertension, and iatrogenic hypothyroidism.

When starting treatment, the pet is re-evaluated at 2-week intervals with assessment of clinical signs, renal function tests, and a TT4.

When euthyroidism has been achieved, monitoring visits are recommended after 1 month, 3 months, and twice yearly thereafter via laboratory testing as outlined below (**Laboratory Analysis**).

Laboratory Analysis

Laboratory monitoring should include a complete blood count, serum biochemistry profile, TT4 concentration, and urinalysis.

With regard to TT4 concentration:

- The biochemical therapeutic endpoint is a TT4 concentration within the lower half of the laboratory reference range.
- Values *below the reference range* indicate hypothyroidism, which has been linked to progression of renal disease and increased mortality.
- Values in the *upper 50% of the reference range* may result in fT4 concentrations above the reference range, causing persistent signs of hyperthyroidism.
- Timing of blood draw with relationship to time of dosing with methimazole is ***not*** a factor when assessing response to treatment.[9]

IN SUMMARY

Methimazole (oral and transdermal) is a safe and effective medication for the treatment of feline hyperthyroidism when dosed and monitored appropriately. ■

fT4 = free thyroxine; PLO = pluronic lecithin organogel; T4 = thyroxine; TSH = thyroid stimulating hormone; TT4 = total thyroxine

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