OVERVIEW

Treatment Choices for Hyperthyroidism in Cats

- Radioiodine ($^{131}$I)
- Methimazole
  - Oral
  - Transdermal
- Carbimazole
- β-adrenergic receptor blockers (β-blockers)
  - Propranolol
  - Atenolol
- Iodinated contrast agent (short-term therapeutic use in cats)$^1$
  - Iopanoic acid
- Propylthiouracil

Drugs that Might Influence Thyroid Testing in Dogs

- Glucocorticoids
  - Prednisone and prednisolone
- Phenobarbital
- Potentiated sulfonamide antibiotics
- NSAIDs
- Iodinated contrast agent (diagnostic use in dogs and cats)$^{1-3}$

COMMON THYROID HORMONES

- Total thyroxine ($tT_4$)
- Free thyroxine ($fT_4$)
- Thyroid-stimulating hormone (TSH)
- Total triiodothyronine ($tT_3$)
- Free triiodothyronine ($fT_3$)

TREATMENT CHOICES FOR HYPERTHYROIDISM IN CATS

Radioiodine

Radioiodine ($^{131}$I) actively concentrates in the thyroid gland. The emitted β particles are locally destructive, sparing adjacent tissues and atrophied thyroid tissue. This is the treatment of choice for most hyperthyroid cats.$^4$
Formulation → SC, IV, PO; SC preferred for safety

Dose strategy → Dose may vary depending on treatment facility, with a fixed dose of 4-5 mCi (148-185 MBq), and a dose of up to 30 mCi (1110 MBq) for thyroid carcinomas.4,5
- Absorbed immediately into circulation with a physiologic half-life of 8 days6
- Excreted mainly in urine and feces6
- Hospital stays can range from 3 days to 4 weeks, depending on dose and regional radiation regulations.5

Key Points
- >95% success rate with a single treatment4,5
  - Hormone levels should return to normal by 3 months (range, 2 weeks to 3 months).
- High doses are recommended for treating thyroid carcinomas.5,7
- Serious adverse events include permanent hypothyroidism.
  - Some cats develop iatrogenic hypothyroidism, but it is usually subclinical. If concurrent clinical signs and/or azotemia are present, treatment with levothyroxine may be necessary.5,8,9
- Owners cannot visit during hospitalization and must collect pet’s waste for 2 weeks after discharge.5
- Patients with concurrent disease may benefit from stabilization with medication or diet before definitive therapy.
- A methimazole trial is recommended before131I treatment to determine whether the patient will develop azotemia following 4 weeks of euthyroidism.

Oral Methimazole
Methimazole is a thioureylene drug that blocks thyroid hormone synthesis by inhibiting thyroid peroxidase. It remains the mainstay of medical therapy in the United States.

Formulation → Oral (tablet)

Initial dose → 2.5 mg PO q12-24h (range, 1.25-5 mg/cat)10,12
- Recommend starting low and titrating dose upward as needed based on serum TT4 concentrations
- Administration q24h may be inferior to q12h.13

Dose increments/decrements → 2.5 mg q24h

Key Points
- Most side effects and adverse events (see Oral Methimazole Side Effects & Adverse Events, page 42) are evident within the first 3 months of oral methimazole therapy.
  - Because oral methimazole does not block release of preformed thyroid hormone, it takes 2-4 weeks for serum TT4 concentrations to reach a steady state.
  - Does not shrink goiter; thyroid will continue to grow larger.
  - Considered one treatment of choice if significant pretreatment azotemia is present14
  - Reversible; cats return to a hyperthyroid state within 2 days of drug discontinuation.15
  - If blood dyscrasia, hepatopathy, or facial pruritus or excoriations develops,131I therapy (see Radioiodine, page 40), thyroidectomy, or dietary management can be used as an alternative treatment.16
  - Monitoring CBC, serum chemistry profile, and serum TT4 concentration is recommended every 2-3 weeks for the first 3 months, then every 3-6 months thereafter.10,12
  - Timing of serum TT4 sampling after administration does not matter.17
    - Target range: low end of normal reference range (1-2.5 µg/dL; reference range, 1-4 µg/dL)
  - Potential human teratogen
    - Avoid exposure to product and to urine/feces of cats receiving this medication.12
  - The veterinary-approved product, Felimazole (dechra-us.com), is sugar coated to make tablet administration and swallowing easier. It is available in 1.25-, 2.5-, and 5-mg tablets, which enable more accurate dosing (no need to split tablets).18
  - Labeled products for humans include the trademarked version, Tapazole (pfizer.com), and the generic version, methimazole. These products are available in 5- and 10-mg tablets.19

Transdermal Methimazole
Vehicles include pluronic lecithin organogel (PLO; United States, Canada, Netherlands, UK) and lipophilic (New Zealand).

Formulation → Solution (gel)

Initial dose (extralabel)
PLO → 2.5 mg applied to inner pinnae q12h (range, 2.5-10 mg)13,20
Lipophilic → 10 mg applied to inner pinnae q24h21
  - The same or slightly higher doses than those used for oral methimazole are recommended.21
  - Some studies report q24h administration as effective.21,22

Dose increments/decrements → 2.5-5 mg q24h21
Key Points

- Store product at room temperature to prolong shelf-life.23
- Owners need to wear gloves or a finger cot when applying medication.
- Side effects/adverse events (noted within first 3 months of initiation)
  - Erythema, local irritation13
  - Less GI upset than oral formulation (4%)13
  - Same incidence as oral methimazole (see Oral Methimazole Side Effects & Adverse Events) for neutropenia, hepatotoxicity, and facial excoriations13
  - Not an alternative medication if adversities (other than simple GI upset) occur with oral methimazole13
- Unknown drug stability
  - PLO reportedly stable for 2 weeks per the Professional Compounding Centers of America (PCCA)13
    - Anecdotally appears to work longer10
    - One study reported stability for 60 days at room temperature23
    - Less greasy PLO alternatives such as Lipoderm and

**ORAL METHIMAZOLE SIDE EFFECTS & ADVERSE EVENTS**

- **GI UPSET** (8.8%-24%)10,63
  Anorexia, vomiting, and lethargy, possibly caused by direct stomach irritation; if these signs occur, try discontinuing oral formulation, then restart with lower dose or switch to transdermal formulation.13

- **BLOOD DYSCRASIAS** (3%-9%)10,63,64
  If thrombocytopenia, neutropenia, agranulocytosis, or aplastic anemia occur, discontinue medication; usually reversible within 1 week.
  Other mild hematologic abnormalities (eg, eosinophilia, lymphopenia, lymphocytosis) are usually transient and do not require discontinuation of medication.15

- **FACIAL PRURITUS/EXCORIATION** (2%-15%)15,63
  Severe erythema and pruritus can lead to self-induced excoriation; if this occurs, discontinue medication to reverse.

- **HEPATOTOXICITY** (2%-3%)13,15
  If ALP, ALT, or bilirubin increase with or without clinical signs (eg, anorexia, vomiting, lethargy), discontinue medication; typically reversible.

- **COAGULATION ABNORMALITIES** (2.5%)15,65
  Prolonged PIVKA clotting times can result from inhibition of vitamin K-dependent clotting factor activation and epoxide reductase.65
  Bleeding that cannot be attributed to thrombocytopenia or prolongation of PT or PTT may rarely occur; if so, discontinue medication.

- **POSITIVE ANA** (21.8% incidence, with earlier higher dosing protocols)15
  Unknown clinical significance

- **POSITIVE DIRECT ANTIGLOBULIN TEST** (1.9%)15
  Unknown clinical significance

- **ACQUIRED MYASTHENIA GRAVIS** (rare)66
  If signs of neuromuscular weakness and positive antibody titers to acetylcholine receptors occur, discontinue medication; appears to be reversible with drug discontinuation and/or prednisolone therapy.

- **RENAL EFFECTS** (15%-22%)67,68
  Decreased GFR (hyperfiltration) resulting from hyperthyroidism; can lead to new or worsened azotemia, but clinical decompensation does not necessarily occur.14,70,71
  - Dose change or discontinuation of medication may not be needed if cat is clinically stable and serum tT4 is not too low.
  - If new azotemia is seen, check whether serum tT4 is in the low or low-normal range and TSH is high (>0.5 ng/mL, functional hypothyroidism); if so, reduce methimazole dose to improve renal perfusion.72

- **IATROGENIC HYPOTHYROIDISM** (all therapies)
  Excessive thyroid suppression, or iatrogenic hypothyroidism, has been associated with azotemia and poor prognosis.8 Iatrogenic hypothyroidism has been reported in ≈20% of cats receiving methimazole72; restoration of euthyroidism will decrease creatinine levels.74 However, in one study, development of azotemia following antithyroid therapy did not result in shortened survival time.74

ALP = alkaline phosphatase
ALT = alanine aminotransferase
ANA = antinuclear antibodies
GFR = glomerular filtration rate
PIVKA = proteins induced by vitamin K absence
PT = prothrombin time
PTT = partial thromboplastin time
TSH = thyroid-stimulating hormone
tT4 = total thyroxine

42 plumbstherapeuticsbrief.com October 2016
Lipoderm Active Max can be refrigerated and are reportedly stable for 6 months.\textsuperscript{24}  
- Lipophilic vehicle reportedly stable for 12 months per the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)\textsuperscript{25,26}  
- PLO formulations may be less effective than oral methimazole (at same doses; 67\% vs 82\% euthyroid at 4 weeks).\textsuperscript{13}  
- Owner compliance may be higher.  
- Could be useful for fractious or uncooperative cats  
- Potential human teratogen  
- Avoid exposure to product and to urine/feces of cats receiving this medication.\textsuperscript{12}  

**Carbimazole**

As a prodrug of methimazole, carbimazole is converted to the active form after absorption. Carbimazole is not available in the United States but is used in Europe, the United Kingdom, Australia, and New Zealand.

**Formulation** → Oral (tablet, sustained-release tablet)  

**Initial dose (extralabel)** → 5 mg PO q8-12h\textsuperscript{27-29}; sustained release (UK only), 10-15 mg PO q24h\textsuperscript{30}  
- **Note:** Usually 2× the methimazole dose\textsuperscript{27}

**Key Points**

- Euthyroid status achieved in 71\% of cats following administration of 15 mg q24h\textsuperscript{36}  
- Potential human teratogen  
  - Avoid exposure to product and to urine/feces of cats receiving this medication.\textsuperscript{12}  
- Side effects/adverse events same as those for methimazole (see **Oral Methimazole Side Effects & Adverse Events**) but anecdotally may be less common with carbimazole as a result of decreased relative bioavailability\textsuperscript{27,31}  
  - Carbimazole is not an appropriate alternative if any adverse events are seen with methimazole.

**β-Adrenergic Receptor Blockers (β-Blockers)**

Some β-blockers, including propranolol, inhibit conversion of tT\textsubscript{4} to tT\textsubscript{3}.\textsuperscript{32} However, because propranolol is a nonselective β-blocker, \(\beta_2\)-receptor inhibition can lead to bronchospasm, especially in cats with airway disease. In addition, propranolol does not seem to substantially affect serum thyroid hormone concentrations in dogs.\textsuperscript{33} Atenolol is \(\beta_1\)-selective and thus preferred for use in cats, especially those with a history of lower airway disease.

**Formulation** → Oral (tablet, extended-capsules, solution), IV (solution; propranolol only)

**Dose for propranolol (extralabel)** → 2.5 mg (up to 10 mg)/cat PO q8-12h\textsuperscript{12}  
- For thyroid storm: 5 mg/cat PO q8h or 0.02 mg/kg IV (over 1 minute)

**Dose for atenolol (extralabel)** → Initially 3.125-6.25 mg/cat PO q12h\textsuperscript{10,12}

**Key Points**

- β-blockers may be beneficial to hyperthyroid patients by decreasing the adverse cardiovascular effects of hyperthyroidism (eg, tachycardia, cardiac arrhythmias).\textsuperscript{34}  
- Can be used short-term (in methimazole-intolerant patients) before definitive treatment (eg, \(\textsuperscript{131}\text{I}\) therapy, thyroidectomy)\textsuperscript{32,35}  
- Side effects/adverse events  
  - Bradycardia, lethargy, depression, impaired atrioventricular (AV) conduction, congestive heart failure (CHF) or worsening of heart failure, hypotension, syncope, diarrhea, hypoglycemia, and bronchoconstriction\textsuperscript{12}  

**Iodinated Contrast Agent (Iopanoic Acid)**

Iopanoic acid is an oral cholecystographic agent that inhibits conversion of tT\textsubscript{4} to tT\textsubscript{3}.\textsuperscript{36} Possible inhibition of thyroid hormone synthesis may occur with partial transient improvement of clinical signs in some patients.\textsuperscript{2} The related compound to sodium ipodate is no longer available.

**Formulation** → Oral (capsules)  

**Initial dose** → 50 mg PO q12h\textsuperscript{1,12}  

**Dose increments/decrements** → 50 mg; up to 200 mg PO q24h\textsuperscript{1,12}
Key Points
- Appears to be ineffective for long-term control of feline hyperthyroidism
- Well-tolerated in cats
  - Possible GI upset
- May be suitable for short-term management before surgery or 131I therapy, particularly when methimazole is not tolerated, in conjunction with other antithyroid treatments, and/or in patients with acute thyrotoxicosis
- Iodine-containing compounds will interfere with 131I therapy and/or thyroid scanning.

Propylthiouracil (Not Recommended)
Propylthiouracil (PTU) was the first drug used for treatment of hyperthyroidism in cats.

Key Points
- High incidence rate of severe adverse events (8%-50%)
- Replaced by methimazole in late 1980s
- Structurally similar to methimazole
- Not considered an alternative medication if side effects are seen with methimazole, but this has not been closely examined

INFLUENCE OF DRUGS ON THYROID TESTING IN DOGS
Several drugs can influence thyroid function test results and potentially lead to misdiagnosis of hypothyroidism in euthyroid dogs. Overt clinical hypothyroidism can actually develop after administration of some drugs. Therefore, thyroid test findings should be interpreted carefully in dogs receiving concurrent medications, especially glucocorticoids, phenobarbital, sulfonamide antibiotics, and NSAIDs.

Glucocorticoids
Endogenous and exogenous glucocorticoids inhibit the hypothalamic-pituitary-thyroid axis and can affect peripheral metabolism of thyroid hormones in dogs.

Key Points
- Increased endogenous cortisol concentrations (as occur in patients with hyperadrenocorticism) can lower tT3 and blunt TSH stimulation results.
- Exogenous glucocorticoids, particularly prednisone and prednisolone, can affect thyroid function test results.
  - Immunosuppressive doses (1-2 mg/kg q12h or higher) significantly decrease tT4 and fT4 concentrations.
  - Long-term administration of anti-inflammatory doses (0.5-1 mg/kg q12h, for >1 month) can decrease tT3 levels with a supranormal tT4 increase after TSH administration.
- In summary, endogenous and exogenous glucocorticoids can result in decreased tT4, tT3, and fT4 concentrations and possibly decreased TSH levels.
- To the authors’ knowledge, clinical hypothyroidism induced by glucocorticoids has not been recognized.

Phenobarbital
Phenobarbital increases metabolic clearance of tT4 and may result in normal or slightly decreased tT4 and fT4 concentrations and increased TSH response.

Key Points
- Clinical hypothyroidism has not been recognized.
- Phenobarbital side effects (eg, lethargy, hypercholesterolemia, weight gain secondary to polyphagia) could mimic clinical signs of hypothyroidism.
- Long-term use of phenobarbital (study doses ranging from 1.3 mg/kg PO q24h to 6.6 mg/kg PO q12h) is more likely to influence thyroid hormone concentrations.
- Thyroid hormone concentrations should normalize within 4-6 weeks after discontinuing phenobarbital.

Potentiated Sulfonamide Antibiotics
Sulfonamide antibiotics inhibit thyroid peroxidase, resulting in decreased thyroid hormone synthesis and secretion.

Key Points
- Includes trimethoprim–sulfadiazine, trimethoprim–sulfadimethoxazole, and zonisamide
- Prolonged treatment may induce clinical hypothyroidism (sulfonamide-induced iatrogenic hypothyroidism) with secondary enlargement of the thyroid.
- Effects are species-specific, dose-dependent, and time-dependent.
• Dogs treated with 15 mg/kg PO q12h for 4 weeks had no effects.\textsuperscript{54}
• Dogs treated with 24-30 mg/kg PO q12h for 6 weeks were affected.\textsuperscript{50,52}
  ▶ Can result in decreased tT\textsubscript{4}, tT\textsubscript{3}, and fT\textsubscript{4} levels, increased TSH levels, and decreased response to TSH stimulation\textsuperscript{52}
  ▶ Thyroid scintigraphy may help differentiate endogenous hypothyroidism from sulfonamide-induced hypothyroidism.\textsuperscript{50}
  ▶ Uptake of pertechnetate by the thyroid will be normal to increased with sulfonamide-induced hypothyroidism and minimal with endogenous hypothyroidism.\textsuperscript{50}
  ▶ The drug-induced hypothyroid state resolves after discontinuation of sulfonamide antibiotic (may take 7 days to several months).\textsuperscript{52,55} If antibiotic treatment cannot be discontinued, treatment of hypothyroidism may be necessary.

**NSAIDs**

NSAIDs may be able to displace thyroid hormones from their protein-binding sites.\textsuperscript{56-58} However, aspirin can decrease serum tT\textsubscript{4}, tT\textsubscript{3}, and fT\textsubscript{4} levels in dogs,\textsuperscript{59,60} which is not consistent with decreased protein binding.

**Key Points**

▶ In one study, carprofen (2.2-3.3 mg/kg PO q12h) reportedly decreased tT\textsubscript{4} and TSH concentrations in dogs.\textsuperscript{61}
  ▶ However, another study found no effect on tT\textsubscript{4}, fT\textsubscript{4}, or TSH concentrations after administration of carprofen (1.7-2.3 mg/kg PO q12h for 60 days) or meloxicam (0.2 mg/kg PO on day 1, followed by 0.1 mg/kg PO q24h for 59 days).\textsuperscript{62}
  ▶ Resultant clinical hypothyroidism from NSAID use has not been reported.
  ▶ Further research is needed to study the effects of NSAIDs on veterinary patients.

NATALIE McLEWEE, DVM, is a resident in small animal internal medicine in the department of clinical sciences at Mississippi State University. Her primary areas of interest include endocrinology and nephrology/urology. Dr. McLewee earned her DVM from Ross University and completed a small animal rotating internship at Friendship Hospital for Animals in Washington, DC.

PATTY LATHAN, VMD, MS, DACVIM (Small Animal), is an associate professor of small animal internal medicine at Mississippi State University. Her primary areas of interest are adrenal function testing, diabetes mellitus, and stress hyperglycemia. Dr. Lathan completed an internship at Mississippi State University, followed by a small animal internal medicine residency at Purdue University.