

Methimazole Trials: What Are They Good For?

Traditionally, many veterinary internists recommended methimazole trials in all newly-diagnosed hyperthyroid cats to evaluate the impact of a euthyroid state on renal function. Methimazole trials help identify, or ‘unmask’, the level of underlying CKD and give a preview of how much renal function change we might expect after treating the hyperthyroidism.

Current trends reflect the belief we’ve maintained at the Feline Hyperthyroid Treatment Center; that is, methimazole trials are unnecessary in cats with minimal to no signs of CKD prior to scheduling I-131 therapy. In this newsletter we explain why, and suggest when testing is useful.

Hyperthyroidism and the Kidneys: A Review

Older cats often have both hyperthyroidism and renal disease. The thyroid disease not only makes it difficult to estimate the degree of renal insufficiency, it may negatively impact renal function as well.

Hyperthyroidism causes a hyperdynamic cardiovascular state, which tends to artificially increase renal blood flow (RBF) and glomerular filtration rate (GFR). When the GFR is increased in HT4 cats with chronic kidney disease (CKD), it may “mask” renal insufficiency by lowering the BUN, and even more dramatically, the creatinine.

Aside from masking renal function, hyperthyroidism seems to contribute to the progression of CKD. During hyperthyroidism, markers of proximal renal tubular damage accumulate in the urine, such as RBP (retinol binding protein) and NAG, a lysosomal glycosidase, which originate in the epithelial cells of renal tubules. These markers decrease again when the hyperthyroidism is cured, suggesting that renal tubular damage occurs, and can be reversed to some degree.

If the T4 is brought back down into normal limits, by any means, the GFR normalizes in cats with no renal disease. In cats with CKD, however, the GFR will fall to the low-normal or subnormal levels expected with moderate renal dysfunction.

It is important to recognize that treating the HT4 does not cause CKD in these cats. The CKD was already present and is simply revealed after the T4 normalizes. Only if the thyroid hormone

drops below normal, and isn’t corrected, does the preexisting CKD potentially worsen.

Methimazole Trials

A methimazole trial helps identify how much preexisting kidney disease is present, and how much worse the renal values may become once the thyroid hormone is reduced to normal, or below. If no marked deterioration in function tests occurs, I-131 may be advisable. We perform methimazole trials when the degree of CKD and the candidacy for I-131 are not clear.

Which Cats Benefit from Methimazole Trials?

Methimazole trials are ideally performed on **newly-diagnosed hyperthyroid cats with significant azotemic CKD (IRIS st 3)**.

We refer to these individuals as “**gray zone**” candidates, or those in whom candidacy for I-131 is in question. Other potential candidates are easier to define without methimazole trials as the following explains.

Candidacy for I-131: 4 Groups

We categorize candidates for I-131 therapy into 4 groups, based in part upon IRIS CKD staging. Establishing candidacy in three of these four categories is typically clear enough without obtaining more information from methimazole trials. Only “gray-zone” cats (st 3 CKD) need more testing to determine the best course.

Good Candidates: No Methimazole Trials

In hyperthyroid cats with no evidence of CKD (or other concurrent illnesses), methimazole trials are not advised.

The chances of unearthing significant renal disease with a methimazole trial, in a cat with no signs of CKD are remote. Therefore, it is ideal to simply treat these cats as soon as the diagnosis of hyperthyroidism is clear.

In fact, methimazole trials could postpone definitive treatment, incur more expense and inconvenience for the owner, and potentially cause drug reactions.

(over)

Acceptable Candidates: No Methimazole Trials

We typically treat hyperthyroid cats in st 1-2 CKD with I-131 without performing methimazole trials.

Even if early CKD (st 1-2) exists, it is usually mild, the progression is gradual, and the cat will be healthier and live longer once the thyroid disease is resolved.

Cats with **UA SG's ≤ 1.040** probably have **some renal insufficiency**, even if not yet azotemic, especially in the face of thyroid disease. Approximately 20-25% of HT4 cats with no preexisting serum renal value abnormalities develop azotemia after successful treatment of the thyroid disease, irrespective of therapeutic modality. Even so, their renal function tests typically don't change more than one IRIS stage, do so within the first month of T4 normalization, and usually remain stable for months (or sometimes years) thereafter. In other words, in cats with early stages of CKD, the true degree of azotemia may 'unmask' and 'bud up' a little, but usually is not severe, and renal degeneration due to aging is typically gradual. Although CKD is somewhat unpredictable, cats in stages 1-2 CKD often have at least 1-4 years of decent quality lifespan after the hyperthyroidism is resolved.

According to Mark Peterson, DVM, ACVIM, Animal Endocrine Center, NYC, "Except for advanced (IRIS Stage 3-4) CKD, the necessity of this approach (methimazole trials) is questionable, given that the treatment for the hyperthyroidism is strongly recommended whatever the outcome. In support of this reasoning, the survival of cats that do develop azotemia is not shorter than those that do not develop azotemia after treatment of hyperthyroidism."

He refers to his recent studies, which show that median survival time of previously non-azotemic cats that developed azotemia after I-131 was not actually shorter than those that didn't.

As long as the owners can **accept** the fact that their aging cat has another disease that they will still need to manage even after the thyroid disease is cured, we routinely treat hyperthyroid cats in st 1-2 CKD with I-131. About 30% of the cases we treat fall into this category and do well after treatment.

"Gray Zone" Candidates: Methimazole Trials ARE Indicated

Moderate CKD (st 3), or "gray-zone" candidates are the only group for whom methimazole trials are advised to help determine candidacy for I-131.

Hyperthyroid cats with moderate azotemia (BUN $\geq 45-50$) and UA SG's < 1.018 are mostly likely in st 3 CKD. The creatinine

level often remains within normal limits in the hyperthyroid state, regardless of the stage of CKD. Therefore, the creatinine is less meaningful in assessing CKD level in HT4 cats.

Cats in stage 3 CKD often exhibit other evidence of overt CKD as well, such as small kidneys, anemia, hypokalemia, hyperphosphatemia, dehydration, elevated urinary SDMA, and profound PU/PD.

A methimazole trial helps identify how much preexisting kidney disease exists, and how much worse the renal values may become once the thyroid hormone is reduced to normal, or below. It thereby helps establish whether the cat is a candidate for I-131 or not. If no marked deterioration in function tests occurs, I-131 may be advisable.

We also consider the severity of the hyperthyroidism before committing to a methimazole trial in these cats. For example, if the T4 is borderline $\leq 3.5 \mu\text{g/dl}$, it may be best to ignore it (not treat it) in a cat with st 3-4 CKD. Maintenance of a mild hyperthyroid state may mitigate the azotemia through the increase in the GFR. On the other hand, in cats with moderate to severe thyroid disease, e.g., T4 ≥ 4 , a methimazole trial is indicated. This is especially true when the thyroid disease is so severe and masking the CKD so much that the full extent of the renal dysfunction cannot be gauged without a methimazole trial.

Poor Candidates

We do not need to do a methimazole trial for cats in severe (st 4) CKD to know that they are poor candidates for I-131.

Stage 4 CKD is usually obvious without a methimazole trial. Both BUN and creatinine are very elevated despite high T4 levels, and the cat invariably has other signs of severe renal impairment, such as worsening anemia, dehydration, electrolyte derangement, and palpably tiny, firm, irregular kidneys. Some may even exhibit uremic breath and oral ulcers in end-stage failure, and are generally lackluster and emaciated even when not markedly hyperthyroid.

We do not encourage owners to proceed with I-131 when there's no hope of returning the animal to a decent quality of life even if the thyroid disease is cured.

Methimazole Trials

Protocol

In order to obtain meaningful information about renal function, the T4 **must** be brought into a normal range, $\leq 2.5 \mu\text{g/dl}$. Depending upon the degree of hyperthyroidism, we typically start with 2.5 mg methimazole orally or transdermally every 12 hours for 3-4 weeks, rechecking thyroid and renal values when

the hormone levels and GFR are stabilized. If the T4 has not dropped to normal or even a little below, the methimazole dose should be increased, and all rechecked in another 3 weeks.

Information Gained

Aside from unmasking the degree of underlying renal disease, a trial also establishes whether the owner is able to administer the medication, and whether the cat will be able to tolerate the methimazole without side effects.

If vomiting, diarrhea, pruritus, scabby facial eruptions, lethargy, or bone marrow suppression occur, the methimazole should be permanently discontinued. For example, if vomiting, anorexia, or diarrhea occur, we would stop the drug altogether rather than changing to the transdermal route, because we believe these signs often represent generalized toxicity rather than simple gastrointestinal irritation or microfloral imbalance seen with an antibiotic. Likewise, continuing the drug at a lower dose when signs of hypersensitivity, such as itchy facial eruptions, are present could result in anaphylaxis. In addition to the serum chemistry screen/T4, we check a CBC no later than 3 weeks after initiating methimazole in order to identify any bone marrow suppression (which may begin even sooner).

If the Methimazole Trial Reveals Poor Candidacy For I-131

If the renal function declines dramatically after methimazole, especially if the cat's clinical condition deteriorates, cats in St 3 CKD are not good candidates for I-131, and other treatment options should be considered. Reversible anti-thyroid therapies such as methimazole, or in a select few, Hill's y/d® may help mitigate the effects of the hyperthyroidism for this cat's remaining lifespan. Sometimes, ignoring the thyroid disease is the best option. And occasionally, when other options have been unsuccessful, we will treat with I-131, and initiate l-thyroxine therapy for life to prevent even low-normal levels of thyroid hormones that could lead to worsened renal function.

When No Anti-Thyroid Therapy Is A Consideration

We consider the level of the hyperthyroidism before committing to anti-thyroid therapy of any kind for cats with severe renal failure. For example, if the T4 is borderline $\leq 3.5 \mu\text{g}/\text{dl}$, it may be best to not treat the thyroid disease. The mild hyperthyroid state may not really be causing much weight loss or other effects seen with more advanced thyroid disease and the 'artificially' increased GFR might lessen the azotemia.

Low-level Methimazole

As the renal disease progresses, under-correcting the hyperthyroidism by lowering the methimazole dose and frequency may increase the GFR and lower the azotemia into a more "livable" range. By titrating the drug we hope to control the azotemia, while reducing the overall impact of the hyperthyroidism on our patient.

Again, Dr. Peterson's thoughts:

"In some of these cats with severe CKD (IRIS Stage 3 or 4), maintenance of a mild hyperthyroid state may give the best short-term clinical result. However, this action is far from ideal for the vast majority of CKD/HT4 cats, and these cats have a very guarded to poor prognosis. In general, the validity of maintaining a cat in a mildly hyperthyroid state is questionable given that uncontrolled hyperthyroidism, in itself, appears to be damaging to renal function".

When Do We Reconsider I-131 in St 3 CKD Cats With Poor Methimazole Trial Results?

Some cats are not optimal candidates for I-131, but for one reason or another have failed other treatment pursuits.

We may reconsider treating "gray zone" candidates with I-131 if :

- the owner simply cannot administer the drug to the cat,
- the cat has ANY side effects to the methimazole,
- the cat won't accept Hill's y/d®,
- thyrotoxic heart disease is more threatening than the other problems,
- or the thyroid disease is severe and beyond the control of any other treatments, in essence a 'runaway train' state of disease.

In the absence of severe concurrent illness, such as stage 4 CKD or neoplasia, in which case we would actively dissuade pursuing I-131, we will reevaluate the possibility of I-131.

Some owners simply wish to pursue the best chance for their cat to have a better quality life, for whatever amount of time he/she has left. Moderately azotemic cats may not be ideal, or even good candidates for I-131, but if other anti-thyroid treatments have been unsuccessful, elimination of the hyperthyroidism via **I-131 may prove to be their only medical option. We do treat some of these cats with I-131.**

(over)



*Future FHTC newsletters
to be sent via email:
Sign up at www.felinehtc.com*

«Endorsement Line»
«Full Name»
«Business»
«Address Line 1» «Address Line 2»
«City» «State» «ZIP Code»

INSIDE: Methimazole Trials: What Are They Good For?

I-131 in Stage 3 CKD Cats Our Approach When All Else Fails ($\leq 5\%$ of the HT4 Cats We Treat)

We give a conservative dose of I-131 in hopes of offsetting the very real possibility of low to low-normal thyroid hormone levels afterwards. We cannot control each individual's radioiodine uptake ability or rate of elimination; therefore, the final T4 level could still end up lower than is ideal. We advise the owners they may need to give thyroxine supplement in these cases, the goal being to keep the T4 level at least above $1.25 \mu\text{g}/\text{dl}$, if not higher ($2\text{-}3.5 \mu\text{g}/\text{dl}$), depending upon the severity of the azotemia.

The lynchpin of success in these uncommon cases is keeping the thyroid hormone well within normal limits after I-131. We may start l-thyroxine within 3-6 days after I-131 in order to prevent an undesirable decrease in T4 levels, and prepare the owner for the fact that their cat will most likely be on the hormone support for the remainder of its life.

It is important for the owners to realize that st 3 CKD is moderate and progressive, that the projected lifespan is limited, and that intensive management of the CKD is crucial for even temporary success.

What Should We Be Telling Our Clients?

Methimazole trials should be reserved for newly-diagnosed hyperthyroid cats with significant azotemia (Stage 3 CKD) in order to help establish candidacy for I-131.

We refer to these individuals as “gray zone” candidates, or those in whom candidacy for treatment with I-131 is in question. Hyperthyroid cats in other stages of CKD are easier to define and treat without this additional testing.

Even with these guidelines, establishing candidacy for I-131 can be complex and every case has its own nuances. We always review your patient's medical records before we confirm their appointment with us, we reevaluate candidacy for I-131 upon physical examination of the cat, and are available to discuss with you prior to referring a case, or at any point in the process.

As always, feel free to contact us!

Faythe Vaughan, DVM and Dennis Wackerbarth, DVM

Upcoming Newsletters:

The Role of cTSH in Thyroid Diagnostics • Etiology of Hyperthyroidism

We're available to consult about these topics any time – please contact us if you have any questions.

Sign up via email at: www.felinehtc.com