Clinical Approach to the Yellow Cat

Thomas K. Graves, DVM, PhD, DACVIM
Department of Veterinary Clinical Medicine
University of Illinois at Urbana-Champaign

Icterus occurs when bilirubin accumulates in the plasma and tissues to the extent that it causes visible yellow discoloration of the sclera, mucous membranes, and skin. This occurs when:

bilirubin > 2 mg/dl  (Normal  0.0–0.3mg/dl )

- Feline Bilirubin Metabolism
  - Bilirubin is a heme breakdown product, produced mostly in the spleen. Carrier proteins transport bilirubin into the liver, where it is conjugated and excreted in the bile.
  - Cats are deficient in glucuronyl transferase necessary for bilirubin conjugation
  - Anorexic cats develop deficiency in protein uptake carriers and intracellular protein ligands for bilirubine
  - Taurine is necessary for bile acid conjugation – deficiency results in cholestasis
  - Bilirubinuria is always significant because there is no renal conjugation of bilirubin in cats, and the renal threshold for bilirubin is higher than that of dogs.

Clinically, we divide causes of jaundice into three large categories – pre-hepatic, hepatic, and post-hepatic

- Pre-hepatic causes
  - Excessive RBC hemolysis
  - Mycoplasma Haemophilus
  - Oxidative injury

- Hepatic Causes
  - Hepatitis
  - Cholangiohepatitis
  - FIP
  - Toxoplasmosis
  - Lymphoma
  - Cellular stress
  - Hepatic necrosis
    - Methimazole therapy

- Post-hepatic Causes
  - Pancreatitis
  - Neoplasia
  - Cholelithiasis
  - Liver flukes
  - Cholangitis
  - Ruptured gall bladder or bile duct

Most common causes of jaundice in cats

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic lipidosis</td>
<td>50%</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>25-40%</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>7%</td>
</tr>
<tr>
<td>FIP</td>
<td></td>
</tr>
</tbody>
</table>
• Diagnosis
  o History
    ▪ anorexia, medications, concurrent illness
  o Physical examination
    ▪ Hypersalivation
    ▪ Liver size
    ▪ Hepatomegaly is common
    ▪ Microhepatica is less common, but could be the result of chronic inflammation and cirrhosis (uncommon in cats)
    ▪ Fundic examination to look for evidence of vasculitis associated with FIP
  o CBC
    ▪ Look for anemia
    ▪ Hemolytic anemia
    ▪ Regenerative, Heinz bodies, mycoplasma, RBC fragments, spherocytes
    ▪ Milder non-regenerative anemia in chronic disease
  o Serum chemistry
    ▪ BUN is made in the liver, and low BUN can reflect hepatic failure
    ▪ Glucose—gluconeogenesis is an important function of the liver, and hypoglycemia can accompany severe liver failure
    ▪ Cholesterol – Liver disease can cause reduced excretion of cholesterol in the bile and can
    ▪ Albumin – manufactured in the liver….is low in severe hepatic failure, and would be normal with hemolytic disease
    ▪ Globulin – Can be elevated with chronic inflammation, and is typically elevated in cats with FIP
    ▪ Bilirubin
    ▪ ALT – A hepatocellular enzyme…elevation is associated with hepatocellular injury
    ▪ ALP – A cholestatic enzyme….even mild elevations are important in cats because of the short half-life
    ▪ GGT – Also a cholestatic enzyme….is sometimes (often) not elevated in hepatic lipidosis
    ▪ Bile acids are probably not necessary because increased bilirubin indicated decreased hepatic function if pre- and post-hepatic causes have been investigated.
  o Urinalysis
    ▪ Severe liver disease can cause isosthenuria
    ▪ Bilirubinuria is never normal in cats
  o Coagulation profile –Necessary because coagulation factors are made in the liver.
  o T4 – hyperthyroidism alone would be unlikely to cause icterus
  o FeLV / FIV – May indicate lymphoma
  o Imaging
    ▪ Radiographs can help assess liver size
    ▪ Ultrasound can suggest (not confirm) lipidosis, neoplasia, cholestasis, pancreatitis
  o FNA cytology, culture
    ▪ FNA results are inconsistent at best, and don’t always correlate well with histopathology.
  o Liver biopsy
    ▪ True cut
    ▪ Surgical
    ▪ Laparoscopic
    ▪ Only after coagulation tests are known
Below are some liver profiles from icteric cats.

**Yellow cat #1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin</td>
<td>3.1</td>
<td>(2.7-3.8 g/dl)</td>
</tr>
<tr>
<td>globulin</td>
<td>6.2</td>
<td>(2.6-5.1 g/dl)</td>
</tr>
<tr>
<td>BUN</td>
<td>19.9</td>
<td>(14-34 mg/dl)</td>
</tr>
<tr>
<td>bilirubin</td>
<td>2.3</td>
<td>(0.0-0.3 mg/dl)</td>
</tr>
<tr>
<td>ALT</td>
<td>359</td>
<td>(1-64 U/L)</td>
</tr>
<tr>
<td>ALP</td>
<td>52</td>
<td>(6-93 U/L)</td>
</tr>
<tr>
<td>GGT</td>
<td>8</td>
<td>(0-3 U/L)</td>
</tr>
<tr>
<td>cholesterol</td>
<td>131</td>
<td>(63-130 mg/dl)</td>
</tr>
</tbody>
</table>

This pattern is typical of cholangiohepatitis, but could occur with FIP as well. The pattern is more hepatocellular injury than cholestatic. In fact, there is no evidence of cholestasis.

**Yellow cat #2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin</td>
<td>3.3</td>
<td>(2.7-3.8 g/dl)</td>
</tr>
<tr>
<td>globulin</td>
<td>4.3</td>
<td>(2.6-5.1 g/dl)</td>
</tr>
<tr>
<td>BUN</td>
<td>19.3</td>
<td>(14-34 mg/dl)</td>
</tr>
<tr>
<td>bilirubin</td>
<td>6.2</td>
<td>(0.0-0.3 mg/dl)</td>
</tr>
<tr>
<td>ALT</td>
<td>109</td>
<td>(1-64 U/L)</td>
</tr>
<tr>
<td>ALP</td>
<td>403</td>
<td>(6-93 U/L)</td>
</tr>
<tr>
<td>GGT</td>
<td>0</td>
<td>(0-3 U/L)</td>
</tr>
<tr>
<td>cholesterol</td>
<td>211</td>
<td>(63-130 mg/dl)</td>
</tr>
</tbody>
</table>

In this cat, the elevation in ALT is mild, but the highly elevated ALP suggests cholestatic disease. This cat had hepatic lipidosis with no other known disorder. Note the GGT, which is considered an indicator of cholestasis, is not elevated. This is sometimes seen in cats with hepatic lipidosis.

**Yellow Cat #3**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin</td>
<td>3.0</td>
<td>(2.7-3.8 g/dl)</td>
</tr>
<tr>
<td>globulin</td>
<td>6.3</td>
<td>(2.6-5.1 g/dl)</td>
</tr>
<tr>
<td>BUN</td>
<td>21.5</td>
<td>(14-34 mg/dl)</td>
</tr>
<tr>
<td>bilirubin</td>
<td>6.2</td>
<td>(0.0-0.3 mg/dl)</td>
</tr>
<tr>
<td>ALT</td>
<td>391</td>
<td>(1-64 U/L)</td>
</tr>
<tr>
<td>ALP</td>
<td>414</td>
<td>(6-93 U/L)</td>
</tr>
<tr>
<td>GGT</td>
<td>29</td>
<td>(0-3 U/L)</td>
</tr>
<tr>
<td>cholesterol</td>
<td>145</td>
<td>(63-130 mg/dl)</td>
</tr>
</tbody>
</table>

This cat has evidence of cholestasis and hepatocellular injury. It could be consistent with several liver diseases, but this cat had infiltrative lymphoma in its liver.
### Yellow Cat #4

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>3.4</td>
<td>(2.7-3.8 g/dl)</td>
</tr>
<tr>
<td>globulin</td>
<td>2.8</td>
<td>(2.6-5.1 g/dl)</td>
</tr>
<tr>
<td>BUN</td>
<td>15.3</td>
<td>(14-34 mg/dl)</td>
</tr>
<tr>
<td>bilirubin</td>
<td>2.7</td>
<td>(0.0-0.3 mg/dl)</td>
</tr>
<tr>
<td>ALT</td>
<td>57</td>
<td>(1-64 U/L)</td>
</tr>
<tr>
<td>ALP</td>
<td>48</td>
<td>(6-93 U/L)</td>
</tr>
<tr>
<td>GGT</td>
<td>1</td>
<td>(0-3 U/L)</td>
</tr>
<tr>
<td>cholesterol</td>
<td>125</td>
<td>(63-130 mg/dl)</td>
</tr>
</tbody>
</table>

The only abnormality here is the elevated bilirubin. This cat had been anorexic for a couple of days.

**Treatment**

- **Nutrition**
  - **This is the most important aspect of therapy**
  - Appetite stimulants and force feeding to not work as well as enteral feeding
  - Esophagostomy tubes work well for this
    - Start using tube 24 hours after placement
    - Most cats need 70 – 100 kcal/kg/day
    - For a sick cat recovering illness, you can calculate the need as 1.25 x basal energy requirement
      - BER = 30 x BW(kg) + 70
    - Commercial diets for use with feeding tubes are available
    - Start slow – first day’s feedings should only be about 20 ml total
    - Always aspirate tube before feeding to make sure there is not food retention in the stomach
    - Always flush feeding tube with water before feeding
    - Maximum volume per feeding is 20 ml/kg
    - Most cats are fed 4 – 6 times a day
    - Cats should be offered food…and tube feeding can be skipped if the cat eats well
    - Tube should be offered food when the cat has been eating well for a couple of weeks and you have good evidence of resolving disease
  - Fluid therapy
    - Necessary for the cat that is dehydrated
    - If a feeding tube is in place and the gut is working, use it for the daily fluid requirement
  - Antibiotics
    - May not be helpful
    - Beta lactams and metronidazole concentrate well in the bile
  - Corticosteroids
    - Can be useful in inflammatory disease
  - Vitamin K
    - Helps restore clotting function
      - Factors II, VII, IX, X are activated by vitamin K-dependent carboxylation reaction
- Ursodiol (Actigall) - 10-15 mg/kg po sid
  - Bile acids are detergents designed to solubilize biliary lipids and to aid in absorption of fats from the intestine.
  - Hydrophobic bile acids are toxic
  - Solubilize cell membranes
  - Bile acids are pro-inflammatory
  - Major bile acids produced by the liver are cholic acid and chenodeoxycholic acid
  - Ursodiol at therapeutic levels replaces normal bile acids
    - Bile is enriched in ursodiol
    - Ursodiol replaces hydrophobic GCDC in humans and protects hepatocyte membranes
    - Replacing taurocholate may not be of great benefit
  - Ursodiol may inhibit the uptake of toxic bile acids at the intestinal level too
  - Ursodiol increases flow of bile
  - Cholehepatic shunting
  - Ursodiol is secreted into bile
  - Ursodiol is an immunomodulator
  - Safety of ursodiol is fairly well established, but could potentially cause taurine deficiency
  - Therapeutic effects are completely unproven in dogs and cats
  - Potentially beneficial in inflammatory dz, hepatotoxicity, intrahepatic cholestasis
  - Contraindicated in extrahepatic biliary obstructions

SAMe, other antioxidants
  - Help restore glutathione, needed for detoxification reactions
  - Can protect from oxidant injury

Lactulose
  - Useful for treating hepatoencephalopathy
  - Traps ammonia in the gut
Feline Diabetes Update

Thomas K. Graves, DVM, PhD, DACVIM
Department of Veterinary Clinical Medicine
University of Illinois College of Veterinary Medicine

Few diseases are as frustrating for a veterinarian as diabetes mellitus. Realistically, control of hyperglycemia is rarely accomplished, and clinical signs of diabetes often persist. The landscape is changing in feline diabetes, however, and as clinicians learn more about new insulin preparations, diets, and treatment monitoring strategies, cats with diabetes may be better controlled.

Insulin Therapy

There are many different types of insulin that vary with species of origin and with chemical modifications and formulations that affect onset and duration of action. Unfortunately, no feline insulin formulation is currently available, so human, bovine, or porcine insulin are used in treating diabetic cats. Data concerning the pharmacokinetics and pharmacodynamics of insulin in the cat are difficult to interpret. Most published studies have been conducted in normal cats, and some have been done in cats with diabetes. In either case, it is difficult to determine the effects of endogenous vs. exogenous insulin. Determinations of potency, time to peak activity and duration of activity, factors that influence choice of doses and dosing intervals, vary widely from cat to cat. In fact, there is no reasonable way to predict the kinetics of an given insulin preparation in any given patient.

The most commonly used insulin preparations in cats are Regular insulin (Humulin-RTM), NPH insulin (Humulin-N™), porcine lente insulins (Vetsulin™), PZI, Insulin glargine (Lantus™), and insulin detemir (Levemir™). Regular insulin is not used for chronic treatment of diabetes in cats, but is commonly used in the treatment of diabetic ketoacidosis.

NPH, PZI, and Lente

NPH is considered an intermediate-acting insulin, and is available as a human recombinant product. NPH is used commonly in cats with diabetes, and is typically given subcutaneously to cats twice daily. Lente insulin uses zinc as a positively charged ion on which to base insulin polymerization. Polymers are absorbed and metabolized slowly so that the onset and duration of lente insulin are extended beyond those of regular insulin. Human recombinant lente insulin has been removed from the United States market and is no longer available for use. Porcine lente insulin, however, has gained in popularity and is the only insulin currently marketed and labeled for use in the cat. Currently available veterinary products are Vetsulin™ (U.S.) and Caninsulin™ (Europe, Australia, Canada). Porcine insulin is dissimilar in amino acid sequence when compared to feline insulin, but it is no more divergent (by 4 amino acids) than is human insulin. Lente is typically given twice daily by subcutaneous injection, and studies in cats show it is a reasonable choice for treating diabetic cats (Martin and Rand 2001). A recent study suggested the duration of porcine lente is shorter than either PZI or glargine (Marshall et al 2008).

Protamine zinc insulin (PZI) has been used extensively in feline diabetes. This insulin preparation was widely available, but was largely removed from the human market in the 1990’s. Recently, PZI preparations marketed for use in cats have once again become available. One product, PZIVet™, a preparation of 90% beef insulin and 10% pork insulin, was removed from the market last year, but PZI is still available from compounding pharmacies. PZI is still a good choice for long-term treatment of diabetes in cats, and is typically given subcutaneously twice daily.

Glargine

Insulin glargine is a genetically engineered insulin analog that has hormonal action identical to native insulin, has no known immunogenicity, and achieves long-lasting glycemic control while minimizing fluctuations in blood glucose concentration in many human diabetics. Glargine is based on human recombinant insulin with a few amino acid substitutions. Glycine is
substituted for an asparagine residue at the amino terminal of the A chain, and two arginine residues are added to the end of the B chain (Figure 1). The result is a shift in the isoelectric point of the insulin molecule so that it is completely soluble at a low pH (around pH 4). The pH of interstitial fluid is approximately 7.4, and when glargine is injected into a patient, the insulin precipitates into hexamers that are inactive. These insulin hexamers are slowly broken down in the body to form active insulin monomers. The result is that the onset is gentle and the duration is long-lived. Because of the difference in pH, glargine cannot be mixed with other insulin formulations. Experience with using glargine in cats is growing (Weaver et al. 2006, Rand 2006), and many clinicians have had good success with its use. Glargine is best used twice daily subcutaneously.

Detemir

Insulin detemir has been used in Europe for several years and was just recently approved for use in the U.S. Rather than having amino acid substitutions (like insulin glargine), insulin detemir is acylated with myristic acid, which allows hexamers to form at neutral pH, and, more importantly, allows the insulin to bind to albumin (Figure 1). This results in a very slow, smooth delivery of insulin such that once daily delivery is all that is needed in many human patients. We have done some preliminary work comparing the pharmacokinetics of glargine, detemir, and regular insulin in cats (Gilor et al., 2008). Figure 2 shows a comparison of the onset of action and duration of glargine vs. detemir in one cat. In this cat, as in others we have studied, detemir is relatively “peakless” and lasts longer than does glargine. In other cats, the duration of glargine and detemir are similar. One advantage of detemir might be that, because it is bound to albumin, it reaches higher concentrations in organs with fenestrated capillaries, especially the liver. This more closely mimics circulation of insulin in normal physiology. We have observed no toxic effects of detemir in a small number of cats we have studied, and it seems reasonable that detemir could be tried if adequate glycemic control is not achieved with other types of insulin.
Non-injectable Insulin Preparations

In addition to the injectable insulin preparations discussed above, oral, nasal, and inhalant insulin preparations are now becoming available, but their use in cats with diabetes may be limited. There are currently at least two oral insulin preparations either approved for use in diabetic people or in the testing stages. Oral insulin has not been used in the past because there was no way to keep insulin from being digested in the gastrointestinal tract before it could be absorbed into the bloodstream as an intact, biologically active molecule. New nanotechnology has allowed for insulin to be encapsulated in tiny spheres that can adhere to a mucosal surface, protect the insulin from digestion, and allow the insulin slowly to be translocated, intact, from the oral cavity or gut to the bloodstream. Oralin™ is an insulin oral spray that is used several times daily. Similarly, Intestulin™ has been tested in human patients, and is taken four times daily with meals. With these oral insulin preparations, large dosages are needed to achieve control of hyperglycemia in people. Insulin nasal sprays and bioadhesive nasal insulin gels are currently being tested. Finally, fine powder inhalant insulin (Exubera™) has recently been introduced for treatment of diabetes in people. There are no reports of the use of non-injectable insulin preparations in cats.

Insulin Dosage and Administration

Regardless of the insulin preparation used, an initial dose of 0.25 U/kg of body weight is recommended. Typically, long-acting insulin preparations have been prescribed at higher initial doses because there may be less chance of causing hypoglycemia with the slower absorption. We have, however, observed insulin-induced hypoglycemia in cats given initial doses of 0.5 U/kg glargine or PZI.

Physiologically, it makes sense to given insulin with meals. Because cats are usually fed free-choice, twice daily insulin injections coincident with meal times are usually not possible. Most insulin formulations for long-term use in cats are given every 12 hours at times that suit the owners’ schedules. The exception may be with determir, as noted above, that may prove to be useful as a once daily insulin in the cat.

Monitoring Insulin Therapy

Blood Glucose Curves

Monitoring therapy can be difficult in cats with diabetes. Because stress hyperglycemia is common in cats, blood glucose concentrations measured during a veterinary visit can be misleading. Blood glucose curves have been used extensively to monitor insulin therapy in the past. There curves are generated by measuring blood glucose every hour for 12- or 24-hour periods following a dose of insulin. Blood is typically collected from an indwelling central venous catheter (to avoid repeated venipuncture) or, sometimes by repeated pricking of the marginal vein of the ear, a procedure well-tolerated by most cats. Glucose concentrations are measured using a hand-held glucose meter, of which many brands are available. Several hand-held blood glucose meters have been studied for use in cats, and all have been suitable. Conventional wisdom has dictated that adjustments in insulin therapy, whether changes in dose, frequency, or type of insulin, only be made based on serial blood glucose measurements. The validity of blood glucose curves has been called into question by several recent studies (Alt et al. 2007, Kley et al. 2004). When glucose curves are evaluated on different days in the same cat, there is very little consistency. Whether evaluation mean blood glucose concentrations, blood glucose nadir, time-to-nadir, maximum blood glucose concentration, or other parameters, variation is wide enough to result in completely different clinical recommendations in the same patient. Blood glucose curves may not be as helpful as was once thought, and other methods of assessing glycemic control are probably more important.

How then are blood glucose curves useful? Veterinary academicians argue as to the existence of the Somogyi phenomenon in cats, but whether some cats experience true insulin-induced hyperglycemia (from a rebound effect in response to hypoglycemia), or whether it is a simple question of insulin kinetics, wide swings reminiscent of the Somogyi effect are possible. For example, a cat receiving insulin might respond quickly with profound hypoglycemia. If the cat
experiences insulin-induced hyperglycemia or if the action of the insulin is short-lived, the cat can return quickly to a hyperglycemic state. In this instance, persistent hyperglycemia and its clinical signs would persist. This might be suspected based on owner reports of signs of hypoglycemia following insulin administration. A blood glucose curve could potentially identify this situation, but could give only a rough estimate of the duration of action of insulin or the appropriateness of a given dose.

Continuous glucose monitoring using small subcutaneously implanted sensors that measure interstitial glucose concentrations have been used to some extent for serial blood glucose determinations in cats, and can be useful in monitoring therapy. These types of glucose sensors are expected to become more readily available and more affordable in the future.

Fructosamine and Glycosylated Hemoglobin

Serum proteins and hemoglobin can be glycosylated extensively in the presence of high concentrations of glucose. Serum fructosamine testing measures glycosylated serum proteins. Because the average half-life of these proteins is around 2 weeks, fructosamine concentrations in the serum reflect average blood glucose concentrations of a 2-3 week period. With red blood cell lifespan being closer to 3 months, glycosylated hemoglobin concentrations in the blood reflect glycemic control over a longer period of time. Serum fructosamine determination is used more commonly than glycosylated hemoglobin measurement to monitor insulin therapy in cats. Serum fructosamine or glycosylated hemoglobin concentrations above the reference interval are indicative of poor glycemic control.

Urine Testing

Urine chemistry test strips are readily available and easy for cat owners to use at home. Urine testing may be most useful in the beginning stages of treatment to detect ketones should they occur. Also, persistently negative urine glucose testing might indicate chronic hypoglycemia. Most cats with diabetes remain hyperglycemic during some parts of the day despite treatment, so urine glucose is usually positive. Insulin dose adjustments should not be made solely based on urine glucose measurements.

Spot Blood Glucose

Because of stress hyperglycemia and difficulty in predicting insulin kinetics in the cat, individual spot blood glucose measurements are of little use in monitoring feline diabetes. A spot blood glucose test can, however, be of value in identifying hypoglycemia.

Clinical Signs

Clinical signs of hyperglycemia (polyuria, polydipsia, appetite changes, weight loss, poor condition, etc.) may be the most useful determinants of glycemic control in cats undergoing insulin therapy.

Insulin Dose Adjustments

Dosages adjustments should be made based on indicators of glycemic control discussed above. In the cat, increases in insulin doses should be done conservative because a small change can have a large effect. We recommend increasing insulin doses by 0.5 to 1 U/cat. Measuring half-units is usually difficult, but should be attempted when relatively small starting doses are being adjusted upwards. Response to a dose adjustment should be evaluated after a week or more of the new dose.

Dietary Therapy

Dietary management of diabetes is currently attracting much attention in the feline medicine world. High-protein, low-carbohydrate diets are being examined by several researchers, and reports suggest that these diets can be helpful in managing cats with diabetes (Zoran 2002, Bennett et al. 2006, Mazzaferrro et al.2003). In one study of 63 cats with diabetes (Bennet et al. 2006), cats fed a low-carbohydrate diet responded better than those fed a moderate-carbohydrate diet, but there was no difference in serum fructosamine concentrations between the
two groups, so solid conclusions cannot be drawn. Decreased body fat and increased insulin sensitivity might be an advantage of using low-carbohydrate diets in cats with diabetes, and it makes sense to avoid diets high in carbohydrates. Although mostly anecdotal, there is plentiful evidence that dietary therapy is beneficial for many diabetic cats, and commercial diets for diabetic cats are widely available. As important as what a cat with diabetes eats, however, is that it eats consistently. Cats do not always accept diet changes readily, so decisions about what type of diet to feed a diabetic cat are often made based on the dietary preference of the cat.

Because many diabetic cats are non-insulin-dependent, some veterinarians initially recommend a diet change with or without use of a sulfonylurea drug for treatment. While this strategy is successful some of the time, it can also be dangerous. Cats treated in this manner are at risk of developing severe ketoacidosis if there is a relative lack of endogenous insulin. Unfortunately, reliable feline insulin assays are not widely available for clinical use, so if following this type of treatment plan, close monitoring for persistence of hyperglycemia and ketonuria is necessary.

References:


Challenging Issues in Hyperthyroidism

Thomas K. Graves, DVM, PhD, DACVIM
Department of Veterinary Clinical Medicine
University of Illinois at Urbana-Champaign

Today’s feline practitioners are well-versed in the pathophysiology, diagnosis, and treatment of hyperthyroidism. This disease continues to be one of the most commonly diagnosed disorders of geriatric cats, and as our knowledge and experience in diagnosing and treating the disease have grown, certain challenges have become apparent. Diagnosis is often straightforward, but cases of occult hyperthyroidism are increasingly recognized and can present diagnostic challenges. Treatment options for feline hyperthyroidism have not changed substantially in recent years, but awareness of adverse effects of treatment has grown, especially regarding the effects of treatment on renal function.

Diagnosis of Occult Hyperthyroidism

Occult hyperthyroidism is a term that describes clinical hyperthyroidism in which measured serum concentrations of TT4 are within the reference range. Measurement of free T4 (FT4) may be a more sensitive in distinguishing cats with occult hyperthyroidism from cats with non-thyroidal disease (Peterson et al. 2001). Some veterinarians rely on measurement of serum concentrations of free T4 as a first-line diagnostic test for feline hyperthyroidism. We do not recommend this practice for the several reasons. First, most hyperthyroid cats have elevated serum concentrations of total TT4 and FT4. Measurement of FT4 has no added benefit in many cats. The greatest problem arises, however, in evaluating sick cats with non-thyroidal illness. For reasons that are not well explained, around 6-10 percent of cats with non-thyroidal illness have false elevations in serum FT4 concentration (Peterson et al., 2001; Mooney et al. 1996). This means that a cat with alimentary lymphoma, for example, which could be confused clinically with hyperthyroidism, has a significant chance of having a misdiagnosis of hyperthyroidism based on the serum FT4 concentration alone. In this hypothetical case the TT4 would probably be low because cats with non-thyroidal illness reliably have low serum concentrations of TT4 (Peterson and Gamble 1990). So, if FT4 is to be used as a diagnostic test for feline hyperthyroidism, it must be interpreted together with the serum TT4 concentration. If the TT4 concentration is low and the FT4 concentration is high, hyperthyroidism is probably not present. If the serum TT4 concentration is in the high end of the normal range and the serum FT4 concentration is high, a diagnosis of hyperthyroidism can probably be made. It should be noted that FT4 assays are fraught with difficulty and are subject to error (Stockigt 2001). While true circulating concentrations of FT4 may more accurately reflect the thyroidal status of a patient than does TT4, measurement of FT4 hormone is more difficult. Furthermore, FT4 assays are not always available. In some cases, occult hyperthyroidism may be best diagnosed through repeated TT4 testing or by use of the tri-iodothyronine suppression test (Graves and Peterson 1994).

The Effects of Treatment on Renal Function

Several studies have shown that treatment of hyperthyroidism can have profound effects of kidney function in cats, and that feline hyperthyroidism can mask underlying chronic renal failure (Graves et al.1994, DiBartola et al. 1996; Adams et al. 1997, Becker et al. 2000). Treatment of hyperthyroidism by bilateral surgical thyroidectomy causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR). The same is true for radioiodine treatment. For these reasons, the wisdom of treating hyperthyroidism in cats with questionable renal function has been questioned. Especially in cats with impaired renal function, the used of methimazole seems an attractive first-line treatment for hyperthyroidism. Treatment with methimazole would be reversible in the event of exacerbation of renal failure. Furthermore, methimazole has actually been shown to have beneficial effects on kidney function in some species. However, since the effects of methimazole on renal function in hyperthyroid cats has not
been studied, treatment recommendations are based on speculation. In fact, we found that methimazole consistently causes a decrease in GFR in hyperthyroid cats, and that the drop can often unmask underlying chronic renal failure (Becker et al. 2000). Fortunately, we were also able to demonstrate a reversal of this effect upon cessation of methimazole therapy. Other investigators have studied the effects of radioiodine treatment on renal function, and have found that it too causes a decline in renal function in hyperthyroid cats.

Because so many cats exhibit declining renal function upon treatment of hyperthyroidism, the currently recommended first-line treatment is methimazole, for the simple reason that it is reversible. If a cat treated with methimazole experiences a severe drop in GFR and develops overt renal failure, the clinician must begin the difficult course of balancing hyperthyroidism and its effects against the effects of renal failure. In some cases, hyperthyroidism cannot be treated at all, and the clinician must just manage weight loss, hypertension, tachycardia, and cardiac disease. In cases in which methimazole does not cause overt renal failure, owners and veterinarians can probably feel more comfortable about pursuing a more permanent treatment such as radioiodine or surgical thyroidectomy.

**Methimazole Trials**

In recent years, investigators have shown consistently that treatment of hyperthyroidism can have profound effects of kidney function in cats, and that feline hyperthyroidism can mask underlying chronic renal insufficiency. Post-treatment renal insufficiency is common, occurring in 17% to 38% of cats treated for hyperthyroidism. Treatment of hyperthyroidism by bilateral surgical thyroidectomy causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR) (Graves et al. 1994). The same is true for radioiodine treatment and methimazole (DiBartola et al. 1996; Adams et al. 1997, Becker et al. 2000). For these reasons, the wisdom of treating hyperthyroidism in cats with questionable renal function has been questioned. Especially in cats with impaired renal function, the use of methimazole is the most logical first-line treatment for hyperthyroidism. Treatment with methimazole can be reversed in the event of exacerbation of renal insufficiency. For this reason, a trial with methimazole is recommended prior to a more permanent treatment for hyperthyroidism (Graves 1997).

Unfortunately, there are few published data to guide decisions concerning methimazole trials. Veterinarians, general practitioners and specialists alike, commonly recommend methimazole trials only for cats with questionable renal function. There is a commonly held belief that cats with well-concentrated urine (urine specific gravity > 1.035) have adequate renal function and do not run a significant risk of post-treatment renal insufficiency and that methimazole trials are not needed in these cats (Garrett 2006; Mooney 2006). There are no published data to support this opinion, and its wisdom should be questioned. First, urine specific gravity is an unreliable predictor of renal function in cats because of the diuretic effects of thyroid hormone. Second, urine specific gravity is not a measure of GFR, but rather an indicator of renal tubular function. We have asked whether hyperthyroid cats with concentrated urine actually do run a significant risk of post-treatment renal insufficiency, and have gathered preliminary data to investigate this clinical problem. We looked at 20 hyperthyroid cats developing overt renal insufficiency within 6 months of radioiodine treatment in our hospital, and compared results with 19 post-treatment cats in which overt renal failure did not develop (Riensche and Graves 2008). 10 (50%) had urine specific gravity measurements greater than 1.035. Three of those cats had urine specific gravity measurements above 1.050. We suspect, therefore, that urine specific gravity should not be used as a predictor of post-treatment renal status in hyperthyroid cats, and that a methimazole trial should be recommended for any hyperthyroid cat that can tolerate the drug.

There are no published studies that have determined the best length of time for a methimazole trial. Studies in which GFR has been measured in cats treated for hyperthyroidism have typically examined renal function before and 30 days after treatment. It is not known whether there is a further decline in GFR after this initial treatment period, or whether the decline
in GFR is permanent. Our opinion is that a 30-day period is adequate, but that is based on our clinical experience rather than on scientific results. It should also be noted that a good response to a trial with methimazole does not guarantee that a given cat will not experience overt renal insufficiency with subsequent radioiodine treatment. In our hospital we have seen several cats with hyperthyroidism well-controlled on methimazole and with well-concentrated urine and normal serum creatinine and urea nitrogen concentrations, that developed overt renal insufficiency shortly after radioiodine therapy. Some have speculated that a more gradual drop in circulating thyroid hormone concentrations with anti-thyroid drugs vs. radioiodine may explain this situation. Also, methimazole may have some renal protective effects in cats as has been shown in other species.

Are There Predictors of Post-Treatment Renal Failure

Despite the recommendation of some experts, there is no strong evidence to support the notion that cats with urine specific gravity measurements about 1.035 are not at risk for renal insufficiency following treatment of hyperthyroidism, but it is unknown whether there are other predictors. Our group has examined many cases of post-treatment renal failure looking for pre-treatment predictors, and we have not been able to find anything that can predict renal failure. Investigators have reported that pre-treatment GFR measurement may be useful as a predictor of post-treatment renal status in hyperthyroid cats (Adams et al. 1997). In one report cats that underwent treatment for hyperthyroidism and did not develop renal insufficiency all had pre-treatment GFR measurements of greater than 2.25 ml/kg/min. The authors concluded that pre-treatment GFR was a valuable predictor of post-treatment renal insufficiency. We looked back at our original published reports of GFR in cats with hyperthyroidism, and found that 3 of 5 hyperthyroid cats experiencing post-treatment renal insufficiency had pre-treatment GFR’s greater than 2.5 ml/kg/min (Graves et al 1994). We found no significant difference between GFR in cats that did or did not experience post-treatment renal insufficiency. Because of these two conflicting reports, it is probably unwise to consider a given cat safe from harm if the pretreatment GFR is >2.25 ml/kg/min. Differences in methods of determining GFR may account for these disparate reports, but we do not believe there is adequate published evidence to rely on GFR measurement to predict post-treatment renal insufficiency in hyperthyroid cats. Furthermore, measurement of GFR in cats is difficult. Most accepted methods of GFR estimation are not available to the majority of small animal practitioners, so a methimazole trial would be considerably more practical.

How is a Methimazole Trial Done?

While the time necessary to see if treatment of hyperthyroidism will cause overt renal insufficiency has yet to be determined, there is adequate evidence to suggest that 30 days is a reasonable time. A common mistake, however, is failure to recheck serum thyroid hormone concentrations during the trial. Because the half-life of T4 in the cat is less than 8 hours, I typically recheck cats one week after starting a trial. If the T4 is not in the lower half of the normal range (optimal for hyperthyroidism control), the dose is increased and the on-month period is started again. Often the dose of methimazole needs to be adjusted to achieve euthyroidism, and the goal is to have euthyroidism for a month, not just methimazole for a month. Because of the danger of developing other side effects to methimazole (e.g. vomiting, hepatopathy, blood dyscrasias) cats should be re-evaluated at 2-week intervals while on a methimazole trial.

How is Post-Treatment Renal Insufficiency Managed?

If removal of excess thyroid hormone is responsible for the decline in GFR seen in cats treated for hyperthyroidism, can post-treatment renal insufficiency be treated by giving T4 supplementation? Figures 2 and 3 show data from 5 cats with post-radioiodine renal insufficiency treated with 0.05 mg of thyroxine given orally twice daily. T4 supplementation for 30 days, as expected, reliably increased the serum concentration of T4. Body weight remained mostly unchanged. In this preliminary study, serum concentrations of creatinine did not decrease
reliably, with 2 of the 5 cats experiencing increases in creatinine despite T4 supplementation. These data provide a hint that T4 supplementation in cats with post-treatment renal failure may prove clinically disappointing with expectations for increases in GFR not being met. Thorough investigation of this treatment strategy is currently underway.

**Transdermal Methimazole**

Recently, compounding pharmacies have offered methimazole, and a variety of other drugs for small animals, in transdermal gels. These gels contain lecithin and pluronic (called pleuronic lecithin organogel or PLO gel), and, until recently evidence of the effectiveness of transdermal methimazole was anecdotal. One study showed that absorption of a single dose of methimazole was poor when compared to oral or intravenous routes (Dr. Trepanier's lab at University of Wisconsin) (Hoffman et al. 2002). Investigators at Louisiana State performed a retrospective study of 13 hyperthyroid cats treated with transdermal methimazole at doses ranging from 2.5 mg once a day to 10 mg BID, and found that clinical signs improved and serum T4 concentrations decreased significantly (Hoffman et al. 2003). No adverse effects were reported in that study. Most recently another study was done (Sartor et al. 2004) which contained the most useful results to date. 44 cats were studied; 17 were treated with oral methimazole, the 27 received transdermal drug. Cats treated orally were euthyroid by 2 weeks, while cats receiving transdermal methimazole were not. There was, however, no difference in euthyroidism between two groups at 4 weeks. More GI side effects were observed in the in oral group (24% vs. 4%). The two treatment groups had equal incidence of hepatotoxicity, leukopenia, and facial excoriation.

We have a large number of feline patients at the University of Illinois being treated with transdermal methimazole. Most of these cats do well clinically, and owners seem generally pleased with this route of administration.

**Frequency of Methimazole Administration**

It has been a fairly common practice to administer methimazole once daily in some cats when twice daily dosing is inconvenient. Lauren Trepanier’s group at the University of Wisconsin studied the efficacy and safety of giving an entire day’s dose at once, and found that it was less effective in controlling hyperthyroidism than when the dose was divided BID (Trepanier et al. 2003). After two weeks of treatment, only 54% of cats receiving 5 mg methimazole once daily were euthyroid, whereas 87% of cats receiving 2.5 mg methimazole BID were euthyroid.

While once daily dosing of methimazole is not advised, carbimazole, a pro-drug that is converted to methimazole, might be a useful once daily alternative. The use of carbimazole in cats with hyperthyroidism is well-established, and a recent report (Frenais et al 2008) described a controlled release carbimazole formulation that appears effective as a once daily dose. The product is marketed as Vidalta™ in Europe, and U.S. veterinarians may well have this drug available in the future.

**Measurement of Feline TSH**

Measurement of serum concentrations of thyrotropin (TSH) is a mainstay of diagnosis of thyroid disorders in people, and assays have been available for use in dogs for more than a decade. Recently, investigators have begun evaluating canine TSH assays for use in cats (Graham et al., 2000; Otero et al. 2002); Wakeling et al. 2006). As expected, serum concentrations of TSH are reportedly very low in cats with hyperthyroidism, but caution should be exercised in interpreting canine TSH assays used in feline serum. Our personal experience using a canine-specific TSH assay to detect TSH in cats has yielded inconsistent results. Recently, Duncan Ferguson and colleagues have cloned the feline TSH protein and have begun development of a feline-specific immunoassay (Rayalam et al. 2006A and 2006B). This assay may eventually become an important tool in the diagnosis and management of thyroid disorders in cats.
Risk Factors for Hyperthyroidism

The underlying cause of feline hyperthyroidism is, unfortunately, still not known. In addition to the original epidemiological survey done by Scarlett et al. (1988), two other recent reports have tried to identify risk factors. The results have been discordant.

  - flea sprays, indoors, herbicides, fertilizers, canned food
  - Siamese low risk
  - risk factors of Scarlett et al not identified
  - Siamese and Himalayan decreased risk
  - no significant environmental factors found
  - increased risk in cats that prefer fish or liver and giblets flavored canned food
  - Siamese not at decreased risk

Fructosamine in Hyperthyroid Cats

Determination of serum concentrations of fructosamine is commonly used to monitor glycemic control in cats. Diabetes mellitus and hyperthyroidism are both diseases of older cats, and they can occur in combination. Recent studies have shown that care must be taken in interpreting fructosamine measurements in hyperthyroid cats.

  - Serum fructosamine is decreased in hyperthyroid cats
  - Radiiodine treatment results in an increase in fructosamine
- Reusch and Tomsa, *JAVMA*, 1999
  - 50% of hyperthyroid cats have low fructosamine
- Conclusions
  - Accelerated protein turnover lowers fructosamine in hyperthyroid cats regardless of blood glucose.
  - Fructosamine is not a useful indicator of glycemic control in cats with hyperthyroidism.
  - Fructosamine cannot be used to different between diabetes and stress-induced hyperglycemia in hyperthyroid cats

Survival in Feline Hyperthyroidism:

- Predictors of Survival
  - age at diagnosis
  - sex
- Most cats die of renal failure
- 5 year survival
  - 10yo female - 42%; 10yo male - 28%
  - 13yo female - 25%; 13yo male - 13%
  - 16yo female - 11%; 16yo male - 4%
  - No difference in platelets, PT, APTT, PIVKA in hyperthyroid vs. normal cats
  - Methimazole did not alter PT, APTT, and rarely platelet count or PIVKA

The Free T4 Story

Some veterinarians currently use the serum concentration of free T4 (FT4) as a first-line diagnostic test for feline hyperthyroidism. I do not recommend this practice for the following reasons:

1. Most hyperthyroid cats have elevated serum concentrations of total T4 (TT4) and FT4. Measurement of FT4 has no added benefit in these cats.
2. It is true that most cats with occult hyperthyroidism have elevated serum concentrations of FT4 in the face of normal TT4 concentrations. FT4's sensitivity, therefore, is slightly higher than that of TT4. However, the problem arises in evaluating sick cats with nonthyroidal illness. For reasons that are not understood (at least not by me), around 10 percent of cats with nonthyroidal illness have false elevations in serum FT4 concentration (Mooney et al. 1996; Peterson et al. 2001). This means that a cat with alimentary lymphoma, for example, which could be confused clinically with hyperthyroidism, has a 10 percent chance of having a misdiagnosis of hyperthyroidism based on the serum FT4 concentration alone. In this hypothetical case the TT4 would be low since cats with nonthyroidal illness reliably have low serum concentrations of TT4. So, if FT4 is to be used as a diagnostic test for feline hyperthyroidism, it must be interpreted together with the serum TT4 concentration. If the TT4 concentration is low and the FT4 concentration is high, hyperthyroidism is not present. If the serum TT4 concentration is in the high end of the normal range and the serum FT4 concentration is high, a diagnosis of hyperthyroidism can reasonably be made.

It should also be noted that physical examination and historical findings are the most important tests of all. Some practitioners simply rely on serum FT4 concentration as part of a routine geriatric screening panel. If a serum FT4 concentration is slightly elevated, and no goiter has been palpated, the test, together with a serum TT4 determination should probably simply be repeated at a later date. If clinical signs of hyperthyroidism are present, a T3 suppression test would probably be most definitive in ruling out hyperthyroidism.

References


Case 1: A 14-year-old cat with acute onset of blindness

A 14 year old, male intact, DSH cat is presented for acute onset of blindness. There are no other striking historical findings. Physical examination findings reveal a 4/9 body condition score, heart rate of 180, normal mucous membranes, normal hydration, possibly small kidneys on palpation, and a 3/6 systolic murmur with the point of maximal intensity at the left sternal border. Ocular examination reveals bilateral retinal detachment. Palpation of the central neck revealed a small goiter most easily palpable on the left lobe of the thyroid gland.

The initial workup included: urinalysis, chemistry profile, CBC, total T4, thoracic radiographs, and systolic blood pressure measurement.

Results:

Urinalysis:
- Color – pale, clear
- Protein – negative
- Glucose – 1+
- Bili – negative
- Ketones – negative
- Specific gravity – 1.021

CBC (reference interval in parentheses):
- Hct – 44%
- WBC – 22.8 x 10^3 (5.5 – 19)
- Segs – 84%
- Bands – 0%
- Lym – 5%
- Eos – 1%
- Mono – 10%

Chemistry Profile (normal ranges indicated)
- Albumin – 3.0 g/dl (2.7-3.8)
- Calcium – 10.9 mg/dl (8.4-10.8)
- Chloride – 114 mEq/L (112-1240)
- Cholesterol – 102 mg/dl (63-130)
- Creatinine – 0.8 mg/dl (0 – 1.5)
- Glucose – 195 mg/dl (65-129)
- Phosphorus – 3.6 mg/dl (4.0-7.0)
- Potassium – 3.9 mEq/L (3.8-5.4)
- Sodium – 155 mEq/L (144-156)
- TCo2 14 mM (13-25)
- T Bili – 0.1 mg/dl (0.0-0.3)
- BUN – 40 mg/dl (14-34)
- ALP – 89 U/L (6-93)
- ALT – 110 U/L (1-64)

Total T4 = 34 nmol/L (17 – 48)
Thoracic Radiography: Evidence of mild cardiomegaly

Systolic Blood Pressure – 260 mmHg

Questions:
- Is the glucosuria significant?
- Is the urine concentrated enough?
- What is the significance of the neutrophilia?
- What is the significance of the hematocrit?
- Does the elevated BUN indicated renal failure?
- Is the hyperglycemia significant?
- Why is the ALT activity increased?
- Does the normal T4 rule out hyperthyroidism?
- Have any causes of systemic hypertension been excluded?
- What is the next diagnostic step

CASE OUTCOME

The following causes of hypertension were considered:
- Systemic hypertension
  - By far the most common cause in cats
- Hyperviscosity
- Vasculitis/Chorioretinitis
  - Immune-mediated
  - SLE
- Sub-retinal hemorrhage
- Coagulopathy

Ruleouts for hypertension in this cat
- Hyperthyroidism
- Chronic Renal Failure
- Hyperaldosteronism
- Pheochromocytoma
- Diabetes does not seem to cause hypertension in cats
  - Senello et al. JAVMA 2003;223:198

Some subtle findings that increased the suspicion for hyperthyroidism were the hematocrit of 44% (abnormally high for a sick, older cat, but commonly found in hyperthyroidism cats), the relative increase in BUN vs. creatinine (increased protein catabolism leads to BUN elevation unrelated to renal function in hyperthyroid cats), and the increased alanine aminotransferase activity (thought to be due to metabolic stress on hepatocytes).

Repeating of the total T4 measurement, free T4, thyroid scintigraphy, and T3 suppression testing were considered to further investigate occult hyperthyroidism.

Further Results:

The free T4 concentration was elevated, and the fructosamine concentration was in the normal range, so a diagnosis of hyperthyroidism was made
Treatment:

The Effects of Treatment on Renal Function

Investigators have shown consistently that treatment of hyperthyroidism can have deleterious effects on renal function in cats, and that feline hyperthyroidism can mask underlying chronic renal insufficiency.\(^1\) Post-treatment renal failure is common, occurring in 17\% to 38\% of cats treated for hyperthyroidism.\(^1,3,4\) Treatment of hyperthyroidism by bilateral surgical thyroidectomy causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR).\(^1\) The same is true for radioiodine treatment and methimazole.\(^2,4\) This clinical problem has led to the use of “methimazole trials” prior to radioiodine or surgical thyroidectomy. Especially in cats with impaired renal function, methimazole is often considered the most logical first-line treatment for hyperthyroidism because it can be reversed if renal failure ensues.\(^4,5\)

Which cats should undergo methimazole trials?

There are many different recommendations for how and when methimazole trials should be performed. Unfortunately, there are few published data to guide these decisions. For example, veterinarians, general practitioners and specialists alike, commonly recommend methimazole trials only for cats with questionable renal function. There is a commonly held belief that cats with well-concentrated urine (urine specific gravity > 1.035) have adequate renal function and do not run a significant risk of post-treatment renal insufficiency and that methimazole trials are not needed in these cats.\(^6,7\) There are no published data to support this opinion, and its wisdom should be questioned. First, urine specific gravity is an unreliable predictor of renal function in cats because thyroid hormone can cause polydipsia and polyuria as a primary effect, regardless of renal function. Second, urine specific gravity is not a measure of GFR, but rather an indicator of renal tubular function. It is unknown if hyperthyroid cats with concentrated urine are at a lower risk of post-treatment renal failure. We looked at 24 hyperthyroid cats developing overt renal insufficiency within 2-3 months of radioiodine treatment in our hospital, 13 (54\%) had urine specific gravity measurements greater than 1.035. Five of those cats (21\%) had urine specific gravity measurements above 1.050 (unpublished data). We suspect, therefore, that urine specific gravity should not be used as a predictor of post-treatment renal status in hyperthyroid cats, and that a methimazole trial should be recommended for any hyperthyroid cat that can tolerate the drug.

How long should a trial run?

There are no published studies that have determined the best length of time for a methimazole trial. Studies in which GFR has been measured in cats treated for hyperthyroidism have typically examined renal function before and 30 days after treatment.\(^1,3,4\) It is not known whether there is a further decline in GFR after this initial treatment period, or whether the decline in GFR is permanent. My opinion is that a 30-day period is adequate, but that is based on clinical experience rather than on scientific results. It should also be noted that a good response to a trial with methimazole does not guarantee that a given cat will not experience overt renal insufficiency with subsequent radioiodine treatment. In our hospital we have seen several cats with hyperthyroidism well-controlled on methimazole and with well-concentrated urine and normal serum creatinine and urea nitrogen concentrations, that developed overt renal insufficiency shortly after radioiodine therapy. Some have speculated that a more gradual drop in circulating thyroid hormone concentrations with anti-thyroid drugs vs. radioiodine may explain this situation. Also, methimazole may have some renal protective effects in cats as has been shown in other species.\(^8,9\)
Are there predictors of renal failure?

Despite the recommendation of some experts, there is no strong evidence to support the notion that cats with urine specific gravity measurements about 1.035 are not at risk for renal insufficiency following treatment of hyperthyroidism, but it is unknown whether there are other predictors. Our group has examined many cases of post-treatment renal failure looking for pre-treatment predictors, and we have not been able to find anything useful. Investigators have reported that pre-treatment GFR measurement may be useful as a predictor of post-treatment renal status in hyperthyroid cats. In one report cats that underwent treatment for hyperthyroidism and did not develop renal insufficiency all had pre-treatment GFR measurements of greater than 2.25 ml/kg/min. The authors concluded that pre-treatment GFR was a valuable predictor of post-treatment renal insufficiency. We looked back at our original published reports of GFR in cats with hyperthyroidism, and found that 3 of 5 hyperthyroid cats experiencing post-treatment renal insufficiency had pre-treatment GFR’s greater than 2.5 ml/kg/min. We found no significant difference between GFR in cats that did or did not experience post-treatment renal insufficiency. Because of these two conflicting reports, it is probably unwise to consider a given cat safe from harm if the pretreatment GFR is >2.25 ml/kg/min. Differences in methods of determining GFR may account for these disparate reports, but we do not believe there is adequate published evidence to rely on GFR measurement to predict post-treatment renal insufficiency in hyperthyroid cats. Furthermore, measurement of GFR in cats is difficult. Most accepted methods of GFR estimation are not available to the majority of small animal practitioners, so a methimazole trial would be considerably more practical.

How is a methimazole trial performed?

While the time necessary to see if treatment of hyperthyroidism will cause overt renal insufficiency has yet to be determined, there is adequate evidence to suggest that 30 days is a reasonable time. A common mistake, however, is failure to recheck serum thyroid hormone concentrations during the trial. Because the half-life of T4 in the cat is less than 8 hours, I typically recheck cats one week after starting a trial. If the T4 is not in the lower half of the normal range (optimal for hyperthyroidism control), the dose is increased and the on-month period is started again. Often the dose of methimazole needs to be adjusted to achieve euthyroidism, and the goal is to have euthyroidism for a month, not just methimazole for a month. Because of the danger of developing other side effects to methimazole (e.g. vomiting, hepatopathy, blood dyscrasia) cats should be re-evaluated at 2-week intervals while on a methimazole trial.

Final Outcome:

The cat showed no signs of renal insufficiency following the methimazole trial and was treated with radiiodine as a permanent treatment for hyperthyroidism. Shortly thereafter, the cat developed overt renal failure. Subsequently, the cat was treated with varying combinations of thyroid hormone replacement and antihypertensive drugs.
Case 2: a 16 year-old cat with constipation, mild glucosuria
and severe electrolyte abnormalities

Ricky is 16-year-old spayed female DSH

Past History:
- Heart murmur detected by RDVM, referred to University of Illinois for echocardiography.
- No history of vomiting, diarrhea, PU/PD, weight loss, or inappetance.
- Ricky had been fed Hills k/d for the past year.
- On physical examination, Ricky was in good body condition, fractious, well-hydrated, with bilateral retinal detachment and a grade 4/6 systolic murmur.
- Systolic blood pressure was 260 mmHg
- Total and free T4 were both normal
- There was very mild azotemia, a serum glucose of 220 mg/dl, ALT of 133 U/L, glucosuria of 50 mg/dl, and proteinuria of 30 mg/dl.
- Echocardiogram was consistent with hypertensive cardiomyopathy, and was treated with 1.25 mg amlodipine once daily.
- Serum fructosamine was 265 umol/L (reference 175 – 400)
- The hypertension resolved within a week of amlodipine therapy, and was still controlled three weeks later, when the chemistry profile and urinalysis were repeated.
- At that time, there was no azotemia, and the urine was concentrated at 1.045, but the glucosuria had increased to 1000 mg/dl, with 30 mg/dl protein in the urine.
- Blood glucose at that time was 175 mg/dl, and the serum fructosamine was 295 umol/L.
- Over the next 2 weeks, Ricky developed constipation, and received several warm water enemas at the RDVM and at home. She was on lactulose at 1 ml PO TID. She became lethargic and anorexic at home 24 hours prior to admission to ICU.

On Presentation:
- BCS 4/9
- Dull and lethargic
- Hydration appeared normal
- Large, firm feces in caudal abdomen
- 3/6 systolic murmur
- Blind

Diagnostics:
- Doppler systolic blood pressure = 125 mmHg
- Urinalysis
  - Spec grav = 1.045
  - pH = 6
  - Protein – 30 mg/dl
  - Glucose – 1000 mg/dl
  - No other abnormalities, no active sediment
- CBC
  - Hct = 29% (reference: 30 – 45)
  - Everything else normal
- Chemistry
  - Phosphorus - 2.9 mg/dl (reference: 4.0 – 7.0)
  - Sodium – 134 mEq/L (reference: 144-156)
  - Potassium – 3.7 mEq/L (reference: 3.9 – 5.4)
  - Chloride – 100 mEq/L (reference: 112-124)
  - Glucose – 167 mg/dl (reference: 65-129)
  - ALT – 94 U/L (reference: 1 – 64)
  - Cholesterol – 219 mg/dl (reference:63 – 130)
Problems:
- Weakness
- Anorexia
- Medically controlled hypertension of unknown cause
- Constipation
- Glucosuria
- Proteinuria
- Hyponatremia
- Hypokalemia
- Hypochloremia
- Hypophosphatemia
- Hypercholesterolemia
- Elevated ALT

Questions:
What is the cause of the hypertension?
Does the cat have diabetes mellitus?
If so, why are the fructosamine results consistently normal?
What are the reasons for the electrolyte abnormalities?
What are possible causes of proteinuria in this cat?
What are possible causes of glucosuria in this cat?
Why is the cat anorexic?
Why is the cat constipated and how should it be treated?

Diagnostic/Treatment Plan and Outcome
We were concerned about hyperthyroidism as a cause of hypertension, even with T4 in the normal range, because it is known that sick cats have falsely lowered T4’s, although the free T4 should have been elevated. Hyperthyroidism is an important cause of hypertension, and there was not evidence of chronic renal failure. The repeat T4 was below the detection limit of the assay, essentially eliminating hyperthyroidism as a possibility.

Hyponatremia, hypokalemia, hypochloremia, and acidosis can be caused by proximal renal tubular dysfunction. Failure of proximal renal tubular reclaiming of filtered solutes can also lead to urinary loss of amino acids, small polypeptides, and glucose. This could explain the glucosuria. The glucosuria was consistent despite unimpressive elevations in blood glucose and normal fructosamine concentrations. To test for proximal renal tubular disease we performed venous blood gases, and measured fractional excretion of potassium, chloride, sodium and phosphorus.
- Sodium 0.09%
- Potassium 26.5%
- Chloride 0.11 percent
- Calcium 0.18%
- Phosphorus 56.5%

These results show appropriate tubular response to the electrolyte disturbances. Venous blood gases were within normal limits. Ricky was treated with LRS, supplemented with KCl. She was given enemas of LRS and started on cisapride for the constipation.
Does Ricky have diabetes?

Glucose Tolerance Testing:
0.5 mg/kg glucose given IV
Samples taken for glucose measurement at 0, 5, 10, 15, 30, 45, 60, 90, and 120 minutes

We interpreted this result as glucose intolerance, and we started her on 1 U Lantus BID.

It took 10 days for Ricky’s electrolyte abnormalities to stabilize, and she began eating and defecating on her own. She went home feeling fine, and continues to do well on insulin, amlodipine, and cisapride. We think the original electrolyte abnormalities were due to a combination of low solute intake and over-zealous water enema administration. We’re really not sure.

Her bill was $3,200.
Case 3: 15-year-old female spayed DLH cat wish weakness

History:
- One-day of lethargy, anorexia, and inability to use the hind legs.
- One-year history of PU/PD
- Diet of Fancy Feast

Physical Exam:
- T = 99°F, P = 148 bpm, R = 36 rpm
- III/VI left parasternal murmur
- L kidney > R kidney
- Profound weakness in rear limbs
- Motor activity present
- Cranial nerves normal
- Non-painful, femoral pulses OK, toes pink

CBC:
- Hct = 27%
- Normocytic, normochromic
- 60,700 retics

Systolic blood Pressure = 160 mmHg

Urinalysis:
- USG = 1.016
- pH = 6
- Protein = 100
- Glucose = 100
- Quiet sediment

Serum Chemistry:
- Creatinine = 350 uM/L mg/dl (90 – 210)
- BUN = 64.1 mg/dl (14 – 34)
- Globulin = 62 g/L (26 – 51)
- Albumin = 43 g/L (27 – 38)
- Phosphorus = 2.8 (0.8 - 3)(0.7-2.6)
- Potassium = 2.7 meq/L (3.8 – 5.4)
- Glucose = 16 mM/L
- Total T4 = 31.5 nmol/L (17 - 49)

Summary of Results:
- Azotemia
- Panhyperproteinemia
- Hyperglycemia
- Hypophosphatemia
- Isosthenuria
- Proteinuria
- Glycosuria

Questions:
1. If this is renal azotemia with dehydration, why is the phosphorus low?
2. What's the reason for the hind limb weakness?
3. Is this cat diabetic?
Subsequent developments
- Intravenous LRS + 24 mEq/L KCL given
- Increased respiratory effort developed over ensuing 8 hours
- Progressed to cyanosis, HR of 88 bpm, temp of 92.7F
- EKG showed only bradycardia and occasional VPC

Recheck of some values:
- Sodium = 154 mEq/L
- Potassium < 2 mEq/L
- Venous pH = 6.887
- Base excess = -11 mmol/l
- pCO2 = 115 mmHg

Assessment
- Mixed acidosis
- Hypoventilation
- Worsening hypokalemia
- Hypernatremia

Our Plan
- Anesthesia and Positive Pressure Ventilation
- Active warming
- KCl infusion
- EKG, temp, blood pressure, pulse ox, and end tidal CO2 monitoring

One Hour Later . . . .
- O2 saturation declines to 90%
- Muffled lung sounds
- Thoracocentesis yielded 300 ml air
- Arterial Blood Gases on 100% O2
  - pH = 7.125
  - pCO2 = 42.1 mmHg
  - pO2 = 144 mmHg
  - Bicarb = 14 mEq/l
  - Base excess = -15 mmol/L

We had initially made a tentative diagnosis of chronic renal failure with secondary hypertension, dehydration and electrolyte loss, but did not know the cause of the hind limb weakness. Hyperglycemia in this cat may have been due to diabetes mellitus, which was consistent with the polyuria, polydipsia, glycosuria and proteinuria, however stress hyperglycemia could not be ruled out. Initial treatment involved intravenous fluid therapy, but within 8 hours of admission the cat’s clinical status had deteriorated. She developed respiratory distress, and electrolyte and venous blood gas analysis revealed mild hypernatremia (sodium 154 mEq/L), severe hypokalemia (potassium < 2mEq/L) and a marked mixed acidosis (pH 6.887, pCO2 115 mmHg, base excess –11 mg/dL). Arterial blood gas analysis performed after thoracocentesis (FiO2 100%) showed pH 7.125, pCO2 42.1 mmHg, pO2 144 mmHg, bicarbonate 14 mmol/L, base excess –15 mmol/L and SO2 98%, indicating metabolic acidosis and relative hypoxemia despite positive pressure ventilation. The acidosis was most likely due to decreased oxygen delivery to tissues secondary to hypoperfusion and hypoxemia with production of acid in anaerobic glycolysis. When the pneumothorax continued and the cat declined further, the owners elected euthanasia.
The gross necropsy findings showed a right adrenal gland tumor. Both kidneys were abnormal, but consistent with chronic disease. A lung tumor was also found, and the pneumothorax may have been due to parenchymal rupture secondary to increased pressure on weakened pulmonary tissue due to the focal lung mass. On histopathology, the adrenal mass was interpreted as a cortical adenoma. The kidneys had interstitial inflammation and membranous glomerulonephritis with glomerulosclerosis and medullary tubular mineralization. We measured the concentration of aldosterone on a banked serum sample. The resting serum concentration of aldosterone was > 3329 pmol/L, consistent with hyperaldosteronism.

Primary hyperaldosteronism is a rare disorder in cats. Although not reported with primary hyperaldosteronism, profound hypokalemia has been associated with respiratory failure in clinical studies of cats. The progressive clinical signs in this cat, from weakness and lethargy to acute respiratory failure, were exacerbated by the initial treatment. The ventilatory failure may have been due to an acute decrease in the serum potassium concentration and intravenous fluid therapy may have exacerbated potassium loss by increasing glomerular filtration rate and delivery of potassium to the distal tubule, where the effects of aldosterone would further enhance potassium excretion. Hypokalemia develops when there is depletion of total body potassium stores or when extracellular potassium is redistributed into cells. Redistribution of extracellular potassium may occur with insulin administration or with a metabolic alkalosis. Decreased potassium intake may occur with inappetance. Potassium loss occurs with most commonly through the kidneys. Osmotic diuresis, diuretics, renal tubular acidosis, and, as in this case, hyperaldosteronism can be the underlying causes of renal potassium loss.

Aldosterone secretion is influenced by serum potassium and renin concentrations. Aldosterone enhances sodium retention and facilitates potassium excretion in the kidney. Clinical signs of hyperaldosteronism are due to sodium retention, and include polyuria, polydipsia and hypertension.

Reports cats with hypokalemia associated with aldosterone-secreting adrenal tumors are rare. This case was reported in the Journal of Veterinary Emergency and Critical Care. For complete information on this case, please see: