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MARCH/APRIL 2024 VOLUME 17 ISSUE 2

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FELINE IDIOPATHIC HYPERCALCEMIA

Joshua W. Tumulty, DVM, DACVIM Dept of Internal Medicine, Long Island Veterinary Specialists



Over the last 2 decades, idiopathic hypercalcemia has emerged to become the most common type of hypercalcemia in cats. Cats with idiopathic hypercalcemia range in age from very young to geriatric, and longhaired cats appear to be over-represented. The diagnosis is established by the laboratory findings of elevated serum total and ionized calcium concentrations with low to low-normal PTH values, after excluding other less common causes of hypercalcemia (primarily cancer).

Because the pathogenesis for idiopathic hypercalcemia remains unknown, treatment for

this condition remains difficult. Response to dietary changes have produced mixed results, and most cats eventually require medical management to control the hypercalcemia. Recently, the utilization of an oral bisphosphonate (i.e., alendronate; Fosamax) has become a more consistent form of therapy.

Total serum calcium cannot be reliably used to predict the metabolically active ionized calcium fraction in cats. An overall diagnostic discordance of 40% during evaluation of hypercalcemic cats was demonstrated in one study. The extent of hypercalcemia known to exist when ionized calcium is measured is underdiagnosed when serum total calcium is used as the screening test for calcium disturbances. Thus, screening cats for calcium metabolic disorders is better served by the measurement of ionized calcium. Once ionized hypercalcemia has been identified, the next step is to determine if the process is PTH-dependent (high PTH from failure to suppress abnormal parathyroid glands) or PTH-independent (PTH is appropriately suppressed as the response of normal parathyroid glands) Figure 1. Compared to dogs, cats have a higher frequency of PTH-independent

Continued on page 4

A NOTE FROM THE EDITOR



Mild weather with not nearly enough sun has been the rule so far on Long Island, but a goodly amount of precipitation has arrived this spring. More than a few basements have been inundated with unwelcome water and more is forecasted. Climate change is the culprit with the western states seeing lots of severe storms, tornadoes, and snow, yet hardly a snowblower has been fired up in our area. An earthquake in early April taught us that Mother Nature is still in control and an uncommon partial eclipse was visible on Long Island on April 8th.

Soon enough, pollens, weeds, and other allergens will add to the itchy, tearing and wheezing sensations that cause discomfort to us and our pets. The Dermatology department has extended hours so that it may better offer its services to our clients and referring veterinarians. Consultations in cases that need direction and appropriate allergic management are available.

Additionally, summer seems to bring on more accidents, rashes, accidental ingestions, gastrointestinal disruptions with subsequent dehydration and injuries of many kinds. LIVS is open for any emergencies that may arise and our extended hours remain as before with each service ready to serve the needs of our clients and those patients referred to LIVS.

The US Senate recently passed in bipartisan fashion, the working dog health and welfare act. Now the house has to act. More than 5000 dogs work in the federal government. They are active in 64 programs, 8 departments and a handful of independent agencies. Common duties include explosives detection, uncovering narcotics, finding missing persons, and safety patrols, among other distinct responsibilities. The bill will ensure these animals receive emergency medical care when needed and are given a proper regimen of exercise, food, water and rest when on the job.

To the relief of our service working dog owners, the canines would be able to enjoy a healthy retirement with medical needs attended to. Dogs have a long and storied history of promoting safety on the home front as well as securing





American freedoms abroad. Dating back to the American Revolution, canines have played critical roads in combat, officially joining the military ranks in World War II. In 1943, one German Shepherd-Collie-Husky mix named "Chips" was even awarded the silver star, the military's third highest medal for bravery. Serving for more than three years on multiple continents, Chips help to save pinned down U.S. forces in Italy and force the surrender of numerous enemy soldiers. During the Korean War dogs performed night patrols to help ambush enemy positions. In Vietnam, canines helped to detect Vietcong traps amid the dense jungle. More recently in Irag and Afghanistan, military dogs' keen sense of smell help to identify IED's.

Today, highly trained canines continue to play an integral role in protecting Americans from backyard threats both from terrorists and Mother Nature. Working dogs at the Federal Bureau of investigation can detect 19,000 different combinations of explosives, a talent that is used to foil terrorist plots at mass gatherings like concerts or sporting events. Unfortunately, they were not present in Israel/Gaza last October 6th nor in Russia this past March.

Search and rescue animals help find people who are lost or trapped following natural disasters, and dogs working with the transportation safety administration patrol the country's airports.

In contrast, an individual who should have known better, was recently given a five-year ban on owning animals after his dog, a Russian Terrier was found suffering with 17 pounds of ungroomed, matted fur; he believed the breed did not need clipping. The matting was a result of the dog being left to sleep outside, with no shelter or dry areas. The environment was very untidy with lots of poop everywhere and very dirty. Some owners just shouldn't own pets.

The photos are of the Long Island University Career Fair recently hosted by LIVS.

All our departments remain fully staffed to serve arriving patients all hours of every day and night. Consultations and appointments can be made by calling (516) 501-1700.

As before we welcome all comments, please submit them to Imarino@livs.org

-Leonard J. Marino, MD, FAAP, LVT

Prosthetics for Small Animals

Continued from front cover

Figure 1 Biochemical parameters expected with common causes of feline hypercalcemia

Biochemical Parameters* Expected with the Common Causes of Feline Hypercalcemia

Disorder	tCa	iCa	Creatinine	Phosphorus	PTH	PTH-rP	Vitamin D**
Renal failure	N, ↑, ↓	N, ↓, occ ↑	1	1, N	occ ↑	N	N, ↓
Primary hyperparathyroidism		1	N, occ ↑	↓,occ ↑	↑, occ N	N	N
Neoplasia (nonosteolytic)	1	1	N, occ ↑	↓,occ ↑	Ļ	1, N	N
Idiopathic		1	N	N	N	N	N
Vitamin D toxicosis	1	1	N, 1	N, 1	Ļ	N	1 T

*These parameters are generalizations. Individual cases may not fit these patterns.

**25-hydroxycholecalciferol

 \uparrow = increased; \downarrow = decreased; N = normal; occ = occasional; PTH = parathyroid hormone; PTH-rP = parathyroid hormone-related protein

hypercalcemia. PTH must always be interpreted along with ionized calcium in the same sample in order to determine appropriateness of the PTH concentration. In those with parathyroid-independent hypercalcemia, malignancy-associated hypercalcemia (MAH) needs to be excluded. MAH most often results from humoral mechanisms as the tumor secretes calcemic substances such as PTHrP into the circulation; local osteolytic hypercalcemia is far less common. A low or undetectable PTHrP does not exclude malignancy as the cause for hypercalcemia since other cytokines that cause calcemia can be elaborated by the tumor instead of PTHrP on occasion. Idiopathic hypercalcemia (IHC), CKD, and neoplasia are the most common and important differential diagnoses to exclude as the cause for parathyroid-independent hypercalcemia. Overt hypervitaminosis D, granulomatous disease, and hypoadrenocorticism are other far less common causes of hypercalcemia in cats. IHC is currently the most common cause of hypercalcemia in cats. While MAH is the number one cause of pathological hypercalcemia in the dog, it occurs far less frequently in the cat. Patients with MAH are usually "sick," as it takes a reasonably large tumor burden to synthesize the messengers that result in hypercalcemia. MAH is less likely to be the diagnosis if the hypercalcemia persists for a long period of time without the cat showing more clinical signs. The less sick the cat is in the face of persistent ionized hypercalcemia, the more the likelihood for the diagnosis to be that of IHC or primary hyperparathyroidism.

In many cases the diagnosis will be obvious upon analysis of history and physical examination. In others, the cause may not be obvious, and further

workup including hematology, serum biochemistry, body cavity imaging, cytology, and histopathology will be necessary. The magnitude of elevation of serum total calcium concentration cannot be used to make a diagnosis, as there is considerable overlap in the degree of hypercalcemia in cats with idiopathic hypercalcemia or other conditions. Nearly ½ of patients diagnosed with IHC are asymptomatic. Other clinical signs have included gastrointestinal signs, including mild weight loss, chronic constipation, vomiting, and decreased appetite. Lower urinary tract signs may be observed, especially if urolithiasis is present. A diagnosis of idiopathic hypercalcemia is made when all other causes of parathyroid-independent hypercalcemia are excluded *Figure 2*.

Management of IHC usually begins with a dietary recommendation to attempt to restore normocalcemia. Treatment with bisphosphonates and glucocorticosteroids usually are reserved for cats with IHC that fail dietary treatment. It has not been determined how much of the hypercalcemia in IHC cats results from too much dietary calcium intestinal absorption, increased bone resorption, reduced renal excretion of calcium, or combinations of these processes. In order to rationally choose a diet that is lower in calcium intake, a complete diet history must be obtained; this includes the cat's primary diet, treats, and any supplements. Once this starting dietary calcium concentration has been determined, the veterinarian can determine which diets would provide less calcium, considering potential comorbid conditions. A veterinary therapeutic renal diet low in calcium (and phosphorus) content may be appropriate for a cat with hypercalcemia and

CKD, but it may not be appropriate to feed a young, otherwise healthy cat a reduced phosphorus, reduced protein diet. Feeding of a high protein and low carbohydrate food similar to what cats would eat in the wild has been recommended to effectively lower serum calcium concentration in some cats with IHC, especially those with low magnitude hypercalcemia. No matter what type of diet is chosen, it is best to feed a wet-only diet to promote urinary dilution and lessen the chance for calcium oxalate stones to form. Unfortunately, in most cats with idiopathic hypercalcemia, dietary therapy will be of minimal long-term benefit, but this management is very unlikely to be harmful. In addition, because many cats with idiopathic hypercalcemia do not show clinical signs for months to years, it is appropriate to try dietary therapy as the first line of therapy at least in cats with mild ionized hypercalcemia. Ionized calcium should be measured following 4 to 6 weeks of feeding the new diet. In some cats, there will be a dramatic decrease in ionized calcium to within the reference range or closer to it. Continued feeding of the newly recommended diet should be continued for another 2 to 3 months to see if any observed benefits are sustained. It is possible that feeding of a new diet will require 2 to 3 months to see maximal benefits, if any. Consideration for treatment with bisphosphonates or prednisolone should be considered for those with high levels of ionized hypercalcemia and/or clinical signs associated with hypercalcemia not responding to dietary change.

The oral bisphosphonate alendronate has become the preferred option to treat IHC cats after dietary modification has failed to restore normocalcemia. Treatment with bisphosphonates may be useful to decrease the magnitude of hypercalcemia in cats with IHC by altering osteoclastic bone resorption. Bisphosphonates reduce the activity and number of osteoclasts following binding to hydroxyapatite. Any food in the stomach can drastically reduce the absorption of alendronate. To maximize intestinal absorption of alendronate, it is recommended that cats be fasted overnight for 12 hours prior to the administration of medication, giving the pills in nothing other than tap water, and then feeding the cat two hours later. A risk of esophagitis and stricture associated with oral bisphosphonate treatment has been reported in humans. The starting dose is usually 10 mg/cat per week initially. It is recommended that a whole tablet be administered, as cut tablets may increase exposure of the esophagus and stomach to adverse effects. Serum ionized calcium levels should be checked at 2 weeks, 1 month, 2–3 months, and then every 4–6 months as long as the ionized calcium concentration remains within normal limits. Most cats seem to have at least a partial calcium-lowering response to alendronate. The drug dose can be raised to up to 30–40 mg per week, as needed. In resistant cats, prednisolone and alendronate can be used together. Administration of glucocorticoids can decrease serum calcium concentration by decreasing

intestinal absorption of calcium, by decreased renal tubular calcium reabsorption, and decreased skeletal mobilization of calcium. Prednisolone is given orally at 5 mg/cat/day for one month before re-evaluation. One disadvantage of prednisolone is that approximately a third of cats will develop secondary diabetes, especially with long-term, high-dose steroid therapy. The long-term safety and efficacy of oral alendronate therapy has not been reported in cats. Mild hypocalcemia is sometimes encountered during oral alendronate treatment of IHC in cats, but overt clinical signs are not usually encountered. Drug-induced esophageal damage (erosive esophagitis and esophageal stricture) and gastritis are of concern in humans taking oral bisphosphonates. An increased risk for bone fracture and osteonecrosis of the jaw (ONJ) has been reported in humans on long-term bisphosphonate treatment, presumably because of the increased brittleness of bone due to bisphosphonate therapy.

Alendronate treatment should be stopped in IHC cats that fail to regain normocalcemia despite 30- to 40-mg weekly doses. It is not known how long oral alendronate treatment should be continued in those IHC cats that have regained normocalcemia for long periods of time. It may not be enough to just monitor calcium and renal function status in IHC cats during treatment interventions. Including baseline long-bone radiographs for all IHC cats being treated with oral bisphosphonates for more than one year, and then yearly thereafter to more readily detect early bone injury that may be developing may need to be considered.

Figure 2 Guidelines for evaluating hypercalcemic cats

- $\label{eq:alpha} \mbox{-Always verify hypercalcemia with a repeat total calcium (tCa) or ionized calcium (iCa) concentration measurement.}$
- •An elevated iCa concentration defines true hypercalcemia.
- •Measure the iCa concentration in any cat with a tCa concentration at or above the upper end of the reference range.
- •Measure the iCa concentration in any cat with renal failure or calcium oxalate urolithiasis, even if its tCa concentration is normal.
- •Severe hypercalcemia mandates immediate attention, and therapy to reduce the serum calcium concentration may be necessary while further diagnostic tests are performed.
- •Most causes of feline hypercalcemia can be diagnosed with a straightforward work-up.
- •Idiopathic hypercalcemia can only be diagnosed after all other causes have been excluded.

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3. Lattimer JC, Selting KA, Lunceford JM, et al. Intraarticular injection of a Tin-117m radiosynoviorthesis agent in normal canine elbows causes no adverse effects. Vet Radiol Ultrasound. 2019:1-8. doi: 10.1111/vru.12757.

Homogeneous Tin (117mSn) Colloid] Veterinary Device for Use in Dogs

NAME: Synovetin OA

Tin (117mSn) stannic colloid in ammonium salt. It is supplied as a 2–4 mCi (74–148 MBq)/mL suspension for intra-articular (IA) injection.

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PRODUCT DESCRIPTION

Synovetin OA^{\oplus} is a conversion electron therapeutic veterinary device comprising a colloidal, sterile suspension with a pH between 6.5 and 9.0 where at least 90% of the particles have a size between 1.5 µm and 20 µm (HORIBA light scatter instrument). The ¹¹⁷⁸Sn emits monoenergetic conversion electrons (significant energies 127–158 keV; emission probability 113%) and imageable gamma radiation (159 keV, 86% abundant). Accompanying low-energy emissions are Augue electrons (<22 keV) and X-rays (<30 keV). The half-life of ¹¹⁷⁰Sn is 14 days. 117mSn decays by isomeric transition to stable ¹¹⁷Sn.

Excipients include ammonium carbonate ((NH₂) 2CO₂), ammonium chloride (NH₄C), ammonium iodide (NH₄I), iodine (L) and trace tin (Sn) salts.

MECHANISM OF ACTION

Synovetin OA^{\oplus} is a veterinary device consisting of a homogeneous tin colloid which emits discrete (<300 µm) low-energy conversion electrons confined to the joint space. The colloid is composed of microparticles (1.5 µm to 20 µm) that are related in the joint space of the dog. The particles are absorbed and retained by synovicytes and macrophages in the synovium, resulting in apoptosis and reduction of inflammatory cells. Elimination of the pro- inflammatory cells reduces inflammation of the joint synovium, thereby reducing pain associated with synovitis. The data, including radiographic evidence, supports use in Grade 1, 2, and 3 osteoarthritis (OA) of the elbow joint.

CAUTION

Federal law restricts this device to sale by or on the order of a licensed veterinarian trained in the use of radioactive veterinary medical products. Use of this product is restricted to facilities with a compatible Radioactive Materials (RAM) license.

INTENDED USE

Synovetin OA® is intended to reduce synovitis and associated pain of canine elbow joints afflicted with osteoarthritis

WARNINGS

Do not exceed 6.0 mCi (222 MBq) of radiation activity per dog per treatment. Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental injection or ingestion by humans.

PRECAUTIONS

Injection should be performed only by a licensed veterinarian skilled in the delivery of intra-articular (IA) injections who is located at a facility that has a RAM license.

Rigorous aseptic technique must be ensured during injection

ROUTE OF ADMINISTRATION

Intra-articular injection. The product must NOT be administered by any other route. Confirmation of needle placement is recommended, whether by anatomical landmarks, fluoroscope, C-arm, ultrasound, or radiography.

DIRECTIONS FOR ADMINISTRATION

Dogs should be appropriately anesthetized or deeply sedated prior to administration to prevent vocalization and resistance to dosing. A 22-ga. needle can be used to inject Synovetin 0Ath directly into the elbow joint. Pain during and after treatment may occur. Administration of non-steroidal anti-inflammatory agents at the labeled dose may help any post-treatment pain.

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MAXIMUM ANNUAL DOSE

Total radiation dose per joint should not exceed 3.0 mCi/joint, with the total body dose not exceeding 6.0 mCi (i.e., two elbow joints during a 12-month period).

ADVERSE REACTIONS

Dogs participating in clinical studies to evaluate safety and effectiveness (n=74 dogs, 97 elbow joints) exhibited no significant adverse reactions when administered Synovetin OA[®]. Disconfort in the treated elbow has been rarely reported in some dogs up to 72 hours after treatment. If adverse events are observed or suspected, please report them by calling Exubrion Therapeutics[®] Customer Service at 1-833-942-1247.

POST-INJECTION CARE

Following administration of Synovetin OA®, the dog can recover with other post-operation animals in the general clinic population. Once the dog has fully recovered from anesthesia, it can be discharged to go home with the approval of the facility radiation safety officer or authorized user. All treatment site policies and license requirements should be observed.

OWNER INSTRUCTIONS FOR POST-TREATMENT CARE

When the level of radiation is determined to be below the established levels for release, the dog can be discharged. The dog will, however, retain a low level of radioactivity in the treated joint(s) for a short period of time. Specific written instructions based on the post-treatment radiation dosimetry for care and proximity to the treated dog will be provided by the radiation safety officer (RSO) or authorized user (AU) of a radioactive materials (RAM)-licensed veterinary hospital to the dog owner. These instructions include information on limiting proximity to the dog in the post-treatment period. If in the judgement of the veterinarian, the dog owners are not likely to comply with the release instructions, the product should not be administered. A RAM-licensed veterinary hospital RSO or AU should contact Exubrion Therapeutics³⁴ if there are specific questions. Apart from the proximity requirements to protect people there is no requirement for restrain to the dog is the radii tcan resume its normal level of activity subject to the distance requirements.

June 2022

MANUFACTURED BY Theragenics Corporation for Exubrion Therapeutics®

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Store in the shipping container at controlled room temperature (10°-30°C or 50°-86°F) until ready to use



CHINESE MEDICINE AND TREATING VOMITING EXPLAINED...

Michel Selmer, DVM, MS, CTCVMP, CVMMP, (Practice Limited to Integrative Veterinary Medicine)



Traditional Chinese Veterinary Medicine (TCVM) offers various approaches to vomiting. Vomiting may be a result of an imbalance or disharmony in the body, and the approach focuses on restoring balance and addressing the underlying causes. Here are some common TCVM approaches to treating vomiting:

Acupuncture involves the insertion of thin acupuncture needles at specific points on the body in an attempt to restore balance. An imbalance in the system results in illness, Specific acupuncture points can be used to restore balance and regulate the gastrointestinal system in an attempt to alleviate nausea and vomiting.

Herbal remedies can be used to help address vomiting by focusing on the root cause. Herbal prescriptions are based on the individual patient's specific symptoms and underlying imbalances in an attempt to help alleviate the clinical signs and restore balance in the gastrointestinal system. Herbs used for vomiting may include ginger, peppermint, fennel, citrus, and cinnamon. These herbs can be soothing to the digestive system, reduce nausea, and improve digestion.

Food therapy emphasizes the importance of diet in maintaining balance within the body. Foods can exacerbate or alleviate symptoms. In the case of vomiting, using food therapy concentrates on consuming feeding bland, easily digestible foods that are gentle on the stomach. Food therapy is tailored to the energies and actions of different food items and their effects on the body. Depending on the imbalance in the body and the patient's individual condition, foods can be used as medicine. At a minimum, it is recommended to avoid feeding greasy, spicy, or overly-rich foods.

It's important to consult a qualified TCM practitioner who can assess your patient's specific condition and provide personalized treatment. They will consider your patient's symptoms, medical history, and overall constitution to develop a suitable treatment plan. The TCM practitioner will also consult with the patient's primary veterinarian if the patient is experiencing persistent or severe vomiting, as it may indicate an underlying medical condition that requires urgent attention.

Please note that a TCVM diagnosis and treatment should be conducted by a certified TCVM practitioner. The patient will then be assessed via the symptoms exhibited, medical history, and physical exam to determine the underlying Chinese patten causing the patient's vomiting so that an appropriate treatment plan can be recommended.

Alternative/Complimentary/Integrative Veterinary care is not intended to replace the services of conventional medicine but instead should be integrated with it. If your patient has persistent or severe vomiting, it's important to rule out any underlying Western medical conditions.





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