

The causes and consequences of feline hypercalcemia

MONTREAL, QC – In general, hypercalcemia is the result of increased gastrointestinal uptake and/or excessive release of calcium from bone, explained Audrey K. Cook, BVM&S, MRCVS, DACVIM, DECVIM-CA, speaking at the ACVIM Forum. The most important considerations in feline medicine include hyperparathyroidism, idiopathic hypercalcemia, chronic kidney disease, and tumours.

Hyperparathyroidism

Primary hyperparathyroidism is usually due to a benign adenoma of one of the four parathyroid glands. The diagnosis is simple if the parathyroid hormone (PTH) concentration is above the upper limit of normal. If the result is unclear, the tests should be repeated after six weeks to determine if ionized calcium and PTH are trending upwards.

Primary hyperparathyroidism in human beings may be managed successfully with calcimimetics. These novel drugs bind specifically to calcium receptors in parathyroid tissue and are a potent inhibitor of PTH release.

Idiopathic hypercalcemia (IHC)

This term describes cats with (generally) mild to moderate hypercalcemia for which no underlying cause can be identified. Dr. Cook said that over the last decade, this syndrome has become the most common cause of hypercalcemia in cats in the U.S. Some of these cats appear clinically normal while others have non-specific signs such as mild weight loss, vomiting, and constipation. Affected cats are predisposed to calcium oxalate urolithiasis due to increased calciuresis.

IHC cats appear to be a heterogeneous group and there is presently no consensus about how to manage these patients or when action is necessary. Ideally, ionized calcium would be maintained at a normal level through modification of net gastrointestinal (GI) uptake or inhibition of osteolysis.

Dr. Cook said that some cats improve on alkalinizing diets; however, these diets generally contain less calcium and phosphorus than maintenance foods and these factors (rather than simply pH) may be beneficial. High-fibre diets also have been suggested on the basis that rapid GI transit may limit calcium absorption. Once again, some cats show a positive response.

Some patients with IHC achieve normal ionized calcium with glucocorticoid therapy, although high doses may be necessary. Dr. Cook stressed that the consequences of chronic steroid administration are substantial and the putative benefits should be weighed carefully against the risks.

Bisphosphonates have been proposed for cats with IHC. These drugs block specific enzyme pathways within osteoclasts, thereby inhibiting bone reabsorption. In theory, a sustained positive response to bisphosphonates seems unlikely if PTH is suppressed, as osteoclast activity in normal individuals is minimal when PTH is scarce.

Chronic renal disease

CKD is listed as a common cause of feline hypercalcemia. As complexed calcium concentrations are often increased in cats with CKD, it is likely that many CKD patients with elevated total calcium are not truly hypercalcemic. However, some cats with CKD do have elevated ionized calcium, in combination with increased PTH concentrations. This is often referred to as tertiary hyperparathyroidism.

Calcitriol appears to inhibit PTH synthesis and has been proposed as a therapeutic option in cats with tertiary hyperparathyroidism. Phosphate, ionized calcium, and PTH concentrations should be monitored regularly and

the calcitriol dose titrated slowly upwards as appropriate. If ionized calcium increases, the drug must be discontinued immediately.

Dr. Cook explained that parathyroidectomy is a recognized treatment for tertiary hyperparathyroidism in human beings who fail medical therapy; however she noted that the technical requirements of this procedure certainly limit its use in feline patients.

Although they are still under investigation, calcimimetics warrant consideration in patients with tertiary hyperparathyroidism. Aberrant PTH release may be regulated effectively without the possible complications associated with calcitriol.

Tumours

Neoplasia is an important cause of hypercalcemia in cats, with lymphoma and squamous cell carcinoma being most common. The mechanism usually is due to release of a fetal protein called PTH-related protein, which mimics the effect of PTH. In most patients, a thorough physical examination, abdominal ultrasonography and thoracic radiographs are adequate to locate the malignancy. Bone marrow aspiration, bone scans, and organ/lymph node aspiration may be necessary in the more challenging cases.

In the short term, hypercalcemia should be managed with saline diuresis, loop diuretics, and injectable bisphosphonates. Hypercalcemia usually resolves rapidly with chemotherapy in cats with lymphoma. Patients with inoperable carcinomas or other non-lymphoid neoplasms may be managed with glucocorticoids and subcutaneous fluids. Chronic bisphosphonate therapy may also be considered.

Consequences of hypercalcemia

Dr. Cook said that the clinical signs associated with hypercalcemia are often vague and non-specific, and include lethargy, vomiting, anorexia, and constipation. Decreased motility may be a factor in GI dysfunction, and might in turn increase calcium uptake by the intestine.

Even small increases in ionized calcium result in marked increase in 24 hour urine calcium excretion. Consequently, many cats present with signs related to calcium oxalate urolithiasis. Dysuria and hematuria may be reported if stones form in the urinary bladder. Abdominal pain and renal compromise may occur with an obstruction in the pelvis or ureter. Because of the close connection between calcium disorders and stone formation, all hypercalcemic cats should be screened for stones with abdominal imaging, and ionized calcium should be measured in any cat with urolithiasis.

Independent of the etiology of hypercalcemia, renal damage is a major cause of patient morbidity. This is somewhat dependent on serum phosphate concentrations, but can occur regardless of the calcium-phosphorus product if hypercalcemia is severe.

Severe hypercalcemia is associated with abnormal neuromuscular function, CNS compromise, and cardiac arrhythmias. Rapid increases in serum calcium can be fatal.

Evaluating the hypercalcemic cat

Dr. Cook suggested that the initial approach to the hypercalcemic cat be influenced by the magnitude of the hypercalcemia, the serum phosphorus concentration, renal status, and the severity of clinical signs. If hypercalcemia is severe (i.e., total calcium > 15 mg/dl), if the calcium-phosphorus product is > 70, or the patient is azotemic, it is appropriate to start supportive care while diagnostic tests are performed.

The diagnostic approach should be guided by patient history and physical examination findings, along with the results of the complete blood count, biochemical profile, and urine analysis. If the serum phosphate is increased,

vitamin D toxicity, osteolytic disease, and renal failure are considered likely. Commercial assays for vitamin D are readily available and should be considered if imaging studies are inconclusive. However, Dr. Cook stressed that it is important to remember that the standard assay measures 25-hydroxycholecalciferol; synthetic vitamin D analogues, and 1,25-hydroxycholecalciferol (i.e., calcitriol) are not detected.

If the serum phosphate level is low or subnormal, hypercalcemia of malignancy or primary hyperparathyroidism should be considered. The next step is the measurement of PTH and parathyroid hormone-related protein. Depending on these findings, cervical ultrasonography may be appropriate.

Finally, a diagnosis of idiopathic hypercalcemia can only be made when all other possibilities have been satisfactorily excluded. CV

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