Calcium Disorders in Dogs and Cats
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Normal Physiology

Calcium is present in two main forms in plasma: ionized (approximately 50%) and protein bound (40%). Ninety percent of the protein bound fraction is bound to albumin. The remaining fraction is neither ionized nor protein bound but is complexed to various anions. Only the ionized fraction is biologically active and its concentration is closely regulated. Clinically significant hypercalcemias and hypocalcemias involve increases or decreases in this ionized fraction. The regulation of serum ionized calcium concentration depends on the interaction of the gastrointestinal tract (GI) and kidneys with vitamin D (1,25- D3) and parathyroid hormone (PTH).

The GI tract plays an important role in the regulation of plasma Ca concentration. Calcium is absorbed in the duodenum and proximal jejunum and absorption is coupled to body needs. The intestine can adapt to low or high calcium diets by increasing or decreasing the efficiency of absorption. Only non-protein bound calcium enters the glomerular filtrate and renal handling of calcium parallels that of sodium with natriuresis (and acidosis) enhancing calcium excretion. Intestinal absorption of PO4 is poorly regulated and most PO4 homeostasis occurs in the kidney. Phosphorus is freely filtered and absorption in the proximal tubules regulates serum levels.

Synthesis of vitamin D results from conversion of ergosterol (plant origin) and 7-dehydrocholesterol (animal origin) to ergocalciferol (D2) and cholecalciferol (D3) respectively. D3 is converted in the liver to 25-D3 and then converted to the active form 1,25- D3 by the enzyme, 1-alpha hydroxylase in the kidney. 1,25-D3 promotes enhanced absorption of Ca and PO4 by the gut, promotes release of Ca and PO4 from bone, and enhances renal reabsorption of Ca and PO4. 1,25-D3 also suppresses the production of PTH in the parathyroid glands. Hypocalcemia, hypophosphatemia, and high PTH concentrations stimulate renal production of 1,25-D3, while hypercalcemia, hyperphosphatemia, renal disease and low PTH inhibit the synthesis of active vitamin D.

PTH is an 84 amino acid polypeptide with a carboxy (-COOH) and amino (-NH3) terminus. The amino terminus is responsible for the biologic activity of the PTH molecule. The amino terminus binds to the PTH receptor on renal tubular cell and results in activation of adenyl cyclase (thereby increasing cyclic AMP concentrations) which leads to Ca retention and PO4 excretion. PTH secretion is controlled primarily by the plasma ionized Ca concentration with hypocalcemia promoting release and hypercalcemia inhibiting release. PTH secretion is also stimulated by decreased concentrations of 1,25-D3 and hyperphosphatemia and decreased by elevated levels of 1,25-D3. PTH in conjunction with vitamin D also causes release of mineral from bone.

A number of factors may alter the distribution of calcium in plasma and these factors must be taken into account when evaluating total plasma calcium concentrations. These include hypoalbuminemia, acid-base status, and the presence of abnormal calcium binding proteins (such as may be present in some cases of myeloma).

Diagnostic Approach

With the advent of assays for intact PTH, ionized calcium and 25-D3, the diagnostic approach to animals with abnormalities in calcium homeostasis has been greatly simplified. Assays for intact PTH are now available that avoid the problems inherent with older PTH assays. These older assays often were directed at detecting only a portion of the PTH molecule (C-terminal, N-terminal, and mid-molecule assays) and gave falsely elevated readings in the face of renal insufficiency as these fragments accumulate with decreased renal clearance. Determination of intact PTH concentrations more accurately reflect parathyroid gland function.

In the past determination of ionized Ca concentration was difficult as the samples had to be handled anaerobically and assayed immediately. Instruments are available today that reliably measure ionized Ca and adjust the concentration for the pH of the sample.

The first step in the evaluation of the patient with hypercalcemia or hypocalcemia is to first repeat the test and verify the abnormality before proceeding to additional diagnostics. The differential diagnoses for hypercalcemia and hypocalcemia are discussed in detail later. Although the lists may seem long, most of the differentials can be ruled-out following the initial history, physical examination, and routine laboratory work (CBC, SMA, UA).

The approach to hypocalcemia is more straightforward than the approach to hypercalcemia and it should be emphasized that primary hypoparathyroidism is the only disease differential diagnosis that results in severe hypocalcemia (<6.5 mg/dl) and mild hyperphosphatemia in the absence of other abnormalities on either the physical examination or routine laboratory work. A presumptive diagnosis of primary hypoparathyroidism can be accurately made on the basis on clinical signs, profound hypocalcemia with no other attributable cause, and a favorable response to treatment with calcium and vitamin D. With the exception of unusual conditions such as vitamin D deficiency and pseudo- hypoparathyroidism, the use of ionized Ca, vitamin D and PTH assays would seem to add little to the diagnostic approach of most patients with hypocalcemia.

In approaching the patient with hypercalcemia the use of these newer assays is very useful in decreasing the number of tests ordered and limiting expense, especially in the asymptomatic hypercalcemic patient where emergency therapy is not warranted. In this group of patients the primary diagnostic dilemma is to rule-out hypercalcemia of malignancy from primary hyperparathyroidism. If the results of the physical examination (remember to perform a rectal examination) and routine lab work fail to identify any abnormality that would lead one to suspect an obvious underlying disease, the use of an intact PTH assay and simultaneous determination of ionized calcium concentration should be the next step in patient evaluation. This approach may also prove to be useful in those patients with hypercalcemia and azotemia. In these patients it is often difficult to determine if the hypercalcemia resulted in renal insufficiency or vice versa. For example, a recent study of chronic renal insufficiency in dogs revealed that 14% of the animals were hypercalcemic (> 12 mg/dl) at the time of presentation. The usefulness of routine determination of vitamin D concentrations in hypercalcemic patients remains to be determined.

The majority of animals with humoral hypercalcemia of malignancy (HHM) have tumors which secrete PTH – related peptide (PTH-rp). PTH-rp binds to the PTH receptor and has the same biologic activity as PTH. Several labs offer PTH-rp assays alone or in combination with PTH and iCa. Animals with HHM will have increases in total and iCa and PTH-rp along with suppressed PTH levels.

This approach can also be used in the patient with symptomatic hypercalcemia. Blood for PTH and ionized Ca can be obtained prior to therapeutic intervention for later assay if required. Additional diagnostics can then performed once the animal has been stabilized.

Differential Diagnosis for Hypocalcemia

A. Lab error. Always recheck before pursuing further diagnostics.

B. Hypoalbuminemia: The ionized calcium is normal so will not have clinical signs.

C. Chronic renal failure: Decreased vitamin D synthesis.

D. Acute renal failure (ethylene glycol): Metabolites of ethylene glycol complex with calcium.

E. Puerperal tetany (eclampsia).

F. Hypomagnesemia: Blunted PTH secretion.

G. Pseudohypoparathyroidism: Defect with PTH receptor or post-receptor abnormality. PTH serum concentration is increased.

H. Vitamin D deficiency.

I. Intestinal malabsorptive diseases: Decreased absorption of calcium and vitamin D.

J. Medications: EDTA, anticonvulsants, citrate.

K. Calcitonin producing thyroid tumor (rare).

L. Phosphate containing enemas (Cats and small dogs).

Differential Diagnosis for Hypercalcemia

A. Lab error. Always re-check.

B. Hypercalcemia of malignancy

1. Lymphosarcoma

2. Anal sac adenocarcinoma

3. Multiple myeloma

4. Bone tumors (rare)

5. Other non-bony tumors (rare)

C. Chronic renal failure

D. Hypoadrenocorticism

E. Young animals (normal)

F. Hypervitaminosis D

1. Overzealous supplementation

2. Rodenticide ingestion ("Rampage" and others)

G. Granulomatous pulmonary disease (Blastomycosis)

H. Granulomatous skin disease

In a recent paper in cats the following disorders were found in patients with hypercalcemia:

1. Neoplasia (21/71)
    a. LSA = 7
    b. SCC = 7
2. Renal failure (18/71)
3. Urolithiasis (11/71)
4. Primary hyperparathyroidism (4/71)
5. Non-parathyroid endocrine disease (4/71)
    a. Hyperthyroidism (2), hypoadrenocorticism (1), diabetes mellitus (3)

6. Diagnostic Approach to Hypercalcemia

A. Rule-out non-parathyroid malignancy and other secondary causes before proceeding to surgical exploration of the neck.

B. Adjust Ca for the albumin concentration

C. Rule out history of vitamin D exposure.

D. Good physical exam. Palpate lymph nodes and always do rectal exam.

E. CBC and biochemistry profile

1. To help rule out other causes of hypercalcemia.

2. Most animals with primary hyperparathyroidism will have hypercalcemia with a normal to low phosphorous.

F. Urinalysis

1. With primary hyperparathyroidism urine specific gravity usually < 1.020. High incidence of urinary tract infections.

2. Calcium oxalate crystals or stones

G. Thoracic and abdominal radiographs to R/O mediastinal mass and organomegaly.

H. Use of PTH assay validated for the dog that measures intact PTH in combination with an ionized calcium concentration will differentiate hypercalcemia of malignancy (low PTH) from primary hyperparathyroidism (PTH normal to elevated). Greatly improves the diagnostic approach to hypercalcemia and reduces the cost to the client.