Disorders of Calcium Metabolism

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The primary endocrinopathies producing alterations in serum calcium metabolism are hyperparathyroidism and hypoparathyroidism. However, the finding of either hypercalcemia or hypocalcemia is not diagnostic for these two diseases as many other causes exist for these biochemical abnormalities.

Normal calcium metabolism

The small, paired parathyroid glands (two glands associated with each thyroid gland) are responsible for maintaining the serum ionized calcium concentration within a very narrow range (total calcium = 8.6-10.7 mg/dl in adults). The only endocrine product of the parathyroids is parathyroid hormone (PTH) which acts on bone, the kidney and the intestines to increase the serum ionized calcium concentration. PTH increases renal reabsorption of calcium and promotes renal phosphorus excretion. PTH also increases osteoclastic activity which mobilizes calcium and phosphorus from bone to increase the serum concentration. In conjunction with active vitamin D_3 (1,25-dihydroxycholeciferol, calcitriol), PTH augments small intestinal absorption of calcium and phosphorous as well. There is an inverse and linear relationship between the ionized serum calcium concentration and PTH concentrations in the blood. As the ionized calcium concentration falls, PTH secretion increases until serum calcium concentration is in the normal range. As the serum calcium concentration increases slightly above normal, PTH secretion is halted and calcitonin is released from the thyroid gland to prevent physiologically inappropriate hypercalcemia.

Hypercalcemia

The differential diagnostic considerations for hypercalcemia include the following (from Feldman, E. Textbook of Veterinary Internal Medicine, 4th ed):

Commonly recognized
- Lymphosarcoma
- Chronic renal failure (mild when present)
- Primary hyperparathyroidism
- Hypoadrenocorticism
- Artifact (lipemia, hyperalbuminemia)
- Laboratory error

Less commonly recognized
- Apocrine cell adenocarcinoma of the anal sac
- Multiple myeloma
- Other solid tumors (Squamous cell carcinoma, thyroid carcinoma)
- Hypervitaminosis D (cholecalciferol rodenticide toxicosis or dietary supplement)

Uncommon to rare

Malignant mammary tumors
Nutritional secondary hyperparathyroidism
Acute renal failure
Blastomycosis (other granulomatous diseases)
Septic bone disease
Hypothermia
Plants with vitamin D like activity (*Cestrum diurnum* (day-blooming jessamine, *Trisetum flavescens* (yellow oat grass), *Lolanum malacoxylon* (nightshade family).

Once hypercalcemia is identified on a biochemical profile it is critical to identify the cause, as treatment, and prognosis vary greatly within this diverse group of hypercalcemic disorders.

Hypercalcemia of malignancy

By far and away the most common cause for hypercalcemia is that seen in association with malignancies (paraneoplasitc syndrome). In the majority of cases the primary tumor is lymphosarcoma. Other neoplasms less often associated with hypercalcemia include apocrine gland adenocarcinoma of the anal sac, and multiple myeloma. Other carcinomas are rarely associated with this paraneoplastic abnormality.

The mechanisms associated with hypercalcemia of malignancy are thought to be: 1) local osteolytic activiey, and 2) a humoral process. Local bone invasion by the tumor cells is thought to result in release of locally active bone resorptive processes leading to hypercalcemia. Most tumors that are thought to cause local osteolysis are of hematologic origin (lymphosarcoma/leukemia complex, multiple myeloma). Locally released prostaglandins and "osteoclast activating factors" (interleukin-1, tumor necrosis factor, lymphotoxin, and others) are also considered important in the mechanism of hypercalcemia.

Humoral factors are thought to be released by neoplastic cells, carried in blood, and act on bone to stimulate bone resorption which leads to hypercalcemia. The humoral product most often mentioned that causes this effect is parathyroid related protein (PTHrP). PTHrP is useful as a diagnostic test in confusing cases of hypercalcemia because it is only elevated in cases of hypercalcemia of malignancy and renal failure.

Primary Hyperparathyroidism

Primary hyperthyroidism is a disease of aged dogs and is very rarely diagnosed in cats. The mean age of onset is 10 years but ranges from 5 to 15 years old. Males equal females in frequency of this disease. The disease

appears to affect large breed dogs more often with Keeshonden at particularly high risk for this disease. Other breeds include German Shepherds, golden retrievers, Laborador retrievers, and Doberman pinschers.

Clinical signs:

Clinical signs of hyperparathyroidism are generally mild and insidious in onset. Three systems are generally affected by the hypercalcemia: the gastrointestinal, renal and nervous systems. GI signs include anorexia, vomiting, constipation and rarely, pancreatitis. Renal signs are characterized by polyuria, polydipsia, and occasionally, signs relative to urinary tract calculi (calcium oxylate, and/or calcium phosphate) such as dysuria, hematuria and pollakiuria. CNS signs are associated with drowsiness, weakness, obtundation and rarely coma. Dogs may be asymptomatic, and are identified because a screening biochemical profile identifies the occult hypercalcemia. Of these signs, the most common are polydipsia, polyuria, listlessness, incontinence, weakness/exercise intolerance, and anorexia. Calcium is highly nephrotoxic and initially impaires renal concentrating mechanisms and later induces necrosis of renal tubules leading to azotemia.

The physical examination of dogs with primary hyperparathyroidism tends to be unremarkable. These tumors are generally non-palpable in dogs , although parathyroid tumors may be palpated during physical exam in the rare cat with this tumor.

Diagnostic plans:

This disease is recognized after a biochemical screen identifies the presence of hypercalcemia. The problem becomes one of identifying which of the mutiple causes for hypercalcemia is producing the problem in an individual patient. Your initial biochemical profile and urinalysis can help to differentiate which of the many causes for hypercalcemia is more likely in a given patient. The total serum calcium is evaluated relative to the serum albumin concentration, the serum phosphorus concentration and the BUN and creatinine concentrations. The mean total serum calcium of dogs with hyperparathyroidism is 15.6 mg/dl and ranges from 12.1 to 23 mg/dl. Hypercalcemia in hyperparathyroidism tends to be very stable with little fluctuations from day to day, and values tend to slowly increase over time.

Sampling errors: You should always repeat abnormal calcium values to be sure sampling errors were not responsible for the elevated value before starting a complicated localizing process in your patients. Marked lipemia, hemolysis, and hemoconcentration can all raise calcium values depending on the method of analysis. Because about half of the total calcium measured in blood is bound to albumin, changes in serum albumin can lead to increased or decreased total calcium values and have nothing to do with parathyroid

abnormalities. The ionized calcium is unaffected by hypoalbuminemia or hyperalbuminemia, however. The effect of albumin concentration on total calcium values is more often important in the presence of hypocalcemia than being a problem in hypercalcemic patients. To correct for the effect that protein bound calcium has on the total calcium value the following formula is used:
Corrected Ca (mg/dl) = measured Ca (mg/dl) - albumin (gm/dl) + 3.5.
As an example, if the measured total calcium was 8.5 mg/dl (hypocalcemic) and the albumin was 2.0 gm/dl (hypoalbuminemic) the formula would be:
Corrected Ca = 8.5 -2 + 3.5 = a corrected value of 10 mg/dl, a normal value. The low value was due to decreased albumin bound calcium in the blood not to some hypocalcemic condition (i.e. the patient has relative hypocalcemia not absolute hypocalcemia.

Determining the serum phosphorous value is helpful in differentiating patients with hyperparathyroidism from other causes of hypercalcemia. In primary hyperparathyroidism, the serum phosphorous is typically low to low normal. The excess PTH results in renal tubular reabsorption of calcium and inhibition of renal phosphorous reabsorption, leading to hyperphosphaturia. The mean serum phosphorous in a series of 72 dogs with hyperparathyroidism evaluated at the University of California was 3.1 mg/dl and ranged from 1.6 to 6.8 mg/dl. Only 5 of 72 had an increased serum phosphorous and all of these dogs had coexisting renal failure induced by chronic hypercalcemia. In spite of the renal compromise in these dogs, the phosphorous did not exceed 6.8 mg/dl.

Always interpret the serum phosphorous concentration in light of the serum calcium and renal function. Hypophosphatemia coupled with hypercalcemia in the absence of renal failure is consistent with primary hyperparathyroidism or hypercalcemia of malignancy. Hyperphosphatemia in the absence of renal failure suggests a non-parathyroid cause for the hypercalcemia (vitamin-D intoxication?). When both hyperphosphatemia and azotemia are present a diagnostic challenge exists. You must differentiate whether the hypercalcemia and hyperphosphatemia are secondary to renal failure, in which case the hypercalcemia is secondary to the renal problem; or whether the renal failure was induced by chronic hypercalcemia, in which case correcting the cause for the hypercalcemia is extremely important as it may lead to correction of the renal problem. Determining an ionized calcium will be helpful in these situations. Dogs with primary renal failure and mild hypercalcemia (calcium 11.5 to 12.5 mg/dl) usually have mild increases in the ionized fraction. In dogs with hyperparathyroidism both the ionized and total calcium values are often markedly elevated.

Renal function: Hypercalcemia predisposes to renal functional compromise that varies from mild (impaired concentration only) to severe (marked

azotemia). The severity is related to whether the calcium x phosphorous product in serum results in precipitation of calcium phosphate in tissues (metastatic calcification). This tends to occur when the product of calcium x phosphorous is greater than 60 to 80. The normal Ca x Phos = 10.0 x 4.5 = 45.

If the BUN and creatinine are elevated it confounds the diagnostic process. You must differentiate the hypercalcemia of malignancy and primary hyperparathyroidism which induces secondary renal failure, from hypercalcemia that follows the development of acute or chronic renal failure alone. Fortunately, most dogs with hyperparathyroidism have normal BUN and creatinine concentrations. Only 10% of dogs with primary hyperparathyroidism are azotemic.

Most dogs with hypercalcemia have dilute urine, often in the 1.008 to 1.015 range because hypercalcemia interferes with ADH function as well as causing direct renal injury. Cystic calculi are found in approximately 30% of dogs with hyperparathyroidism. These calculi are often associated with hematuria, bacteriuria and pyuria. Invariably the stone type is calcium oxylate or calcium phosphate or mixtures of the two.

Ionized calcium concentrations: The biologically active form is the ionized fraction of the total calcium. Most commercial laboratories can now measure the ionized fraction relatively inexpensively which is very helpful in differentiating the various causes for hypercalcemia. In hyperparathyroidism and hypercalcemia of malignancy, the ionized calcium is elevated (normal range 4.93 - 5.65 mg/dl). In chronic renal failure less than 10% have an elevated ionized calcium, with 90% being normal to low. In hypoparathyroidism, eclampsia and pancreatitis the ionized fraction is low.

PTH concentrations: Newly developed methods for measuring PTH have diagnostic usefulness in dogs and cats with hypercalcemic and hypocalcemic disorders. The serum PTH is evaluated in combination with either the total calcium or, ideally, the ionized calcium concentrations. In dogs and cats with hyperparathyroidism, the PTH concentration is high normal or very elevated (4 - 45 pmol/L). In normal animals as the calcium elevates the PTH concentration drops. In hyperparathyroidism all dogs and cats have relatively elevated PTH concentrations compared to their calcium concentrations. In dogs or cats with hypocalcemia and low PTH concentrations a diagnosis of hypoparathyroidism is likely. In dogs with malignancy associated hypercalcemia the PTH is generally very low or non detectable. Unfortunately, a few dogs with malignancy associated hypercalcemia have had normal to mildly elevated PTH concentrations. In both renal failure and primary hyperparathyroidism, the PTH is generally

very elevated so this test does not differentiate between these two, often coexisting, problems. Thus, PTH is useful in the diagnostic evaluation of some hypercalcemic patients, but cannot be used as the sole discriminating criteria.

PTHrP: PTH rP is an abnormal protein secreted by some malignancies that acts physiologically similar to endogenous PTH. It is likely that this protein is what causes most dogs with malignancy associated hypercalcemia to resemble dogs with primary hyperparathyroidism. Work in dogs with lymphoma and apocrine gland adenocarcinomas have shown these tumors do elaborate PTHrP. By simultaneously measuring PTH and PTHrP in dogs suspected to have either primary hyperparathyroidsm or hypercalcemia of malignancy should allow discrimination of these two diseases. In primary hyperparathyroidism, PTH is high normal to very elevated while PTHrP is low. In malignancy associated hypercalcemia PTH levels are low normal while PTHrP levels are high.

Parathyroid ultrasonography: Ultrasound of the parathyroids using high resolution transducers may detect 80 to 95% of parathyroid adenomas in dogs. A smaller percentage of dogs with bilateral hyperplasia of the parathyroids can also be identified.

Radiography: Radiographs of the thorax and abdomen are useful in the evaluation of patients with occult hypercalcemia. Since tumor associated hypercalcemia is much more common than hyperparathyroidism, screening animals with thoracic and abdominal radiographs to search for non-palpable tumors (cranial mediastinum, liver, kidneys, spleen, sublumbar nodes, bones) helps to rule out malignancy associated hypercalcemia.

<u>Diagnostic Evaluation of the Hypercalcemic Patient</u>

In general, the history, physical exam, preliminary lab data (CBC, chemistry profile, UA) will allow diagosis of most of the common causes of hypercalcemia. The most confusing cases generally have either primary hyperparathyroidism or occult neoplasia. In those cases which have totally normal lab work (except for hypercalcemia of course), we often obtain thoracic and abdominal radiographs, aspirate a lymph node (even if it appears normal) and perform a bone marrow biopsy to unequivocally rule-out occult lymphosarcoma. If that is ruled out, we would go to parathyroid ultrasound, submit serum for ionized calcium, PTH and PTHrP analyses. In the absence of the more sophisticated laboratory assays, the clinician must decide if they are going to explore the parathyroids to try and identify an abnormally enlarged gland or treat the hypercalcemia medically to see if it responds rapidly to drug therapy. Patients with hematopoietic tumors generally respond very rapidly to administration of glucocotricoids (24 to 48 hours) with the calcium normalizing or significantly reduced. The primary

disadvantage of this approach is that if lymphosarcoma has not previously been identified, your therapy may make the definitive diagnosis even more difficult. Patients with primary hyperparathyroidism or non-hematopoietic neoplasms generally respond poorly, if at all, to glucocorticoid therapy.

Medical management of severe or life-threatening hypercalcemia

Symptomatic therapy of hypercalcemia is not needed in most patients. Working to identify the cause for the biochemical abnormality is where most of your efforts should be directed. However, if patients are dehydrated, azotemic, weak, have a cardiac arrhythmia, or severe neurological dysfunction, immediate medical management is indicated. Progressive calcification of susceptible tissues, especially the kidney, may occur when the calcium x phosphorus product exceeds 60 to 80. This is common in renal failure but uncommon in other causes of hypercalcemia, and particularly rare in hyperparathyroidism.

Methods to control the hypercalcemia include correcting dehydration, saline diuresis, administration of diuretics (furosemide), administration of glucocorticoids, and mild alkalinization. Correction of volume deficits reduces the hypercalcemia but will not return values to normal. Both furosemide and saline promote renal excretion of calcium and promote gradual reduction in serum calcium concentrations over several days. Glucocorticoids should be withheld until diagnostic efforts to rule-out lymphosarcoma have been completed. Calcitonin has been occasionally administered to lower severe hypercalcemia and is given at 4 to 5 u/kg every 8 to 12 hours SQ. Correcting acidosis by administration of a conservative dosage of sodium bicarbonate (3 meq/kg) IV decreases the ionized fraction in blood and its effects may last for 3 hours or more.

Surgical therapy for primary hyperparathyroidism

The best therapy for hyperparathyroidism is surgical exploration of both thyroids and identification of an enlarged parathyroid. Both adenomas and adenocarcinomas tend to be single, easily identifiable masses associated with one thyroid gland (95% of cases). In less than 5% of cases multiple enlarged parathyroids can be found (multiple adenomas or hyperplastic glands). Consult one of many surgical texts for technique of parathyroid excision. I'm an internist you know!

Postoperative hypocalcemia

Prolonged secretion of PTH by the neoplastic parathyroid results in varying degrees of atrophy of the remaining normal parathyroid tissue. If the presurgical calcium is < 14 mg/dl then the patient is monitored post-operatively for development of significant hypocalcemia (total calcium < 8.5 mg/dl). If the calcium drops to less than 8.5 mg/dl or the dog shows signs of

hypocalcemia then therapy is instituted with vitamin-D with or without calcium supplementation (see section on hypoparathyroidism).

Presurgical calcium concentrations of > 14 mg/dl suggest the patient may have severe parathyroid atrophy and generally, immediate prophylactic treatment with vitamin-D with or without calcium supplementation is begun. Animals are hospitalized for 5 days post-operatively and calcium concentrations monitored once or twice daily. Most patients become hypocalcemic within 2 to 6 days post-operatively. Your goal is to use enough vitamin-D to maintain the serum calcium in the low normal range (8.5 to 9.5 mg/dl). This allows some stimulus for the atrophied parathyroid glands to begin functioning again. As the atrophied glands regain function the calcium and vitamin-D can gradually be discontinued. Once the patient is stable for one to two weeks the vitamin-D is decreased from BID to SID for 2 weeks, then decreased to every third day for 2 weeks then to once weekly for 2 weeks. Always check the total calcium before decreasing the dosage to be sure occult hypocalcemia is not present (<8.0 mg/dl). Once the patient is stable on once weekly vitamin-D for 2 weeks, the drug can be discontinued.

Prognosis

The prognosis for dogs with hyperparathyroidism is generally good if severe renal failure is not also present at the time of diagnosis (BUN > 70 mg/dl). Most of the tumors are benign and even those classified as carcinomas often do not behave like other malignancies. If severe post-operative hypocalcemia can be avoided, these animals can have high quality lives after surgical correction.

Hyperparathyroidism in cats

A total of 8 cats with primary hyperparathyroidism have been described in the literature. Their mean age was 12.9 years with a range of 8 to 15 years. Five of 8 were Siamese and 5 were female. The most common sign was anorexia and lethargy. Four had a palpable mass in the area of the parathyroid. None were hyperthyroid. The only significant biochemical abnormality was the hypercalcemia. One cat had cystic calculi. Serum calcium concentrations ranged from 11.1 mg/dl to 22.8 mg/dl (mean 15.8 mg/dl). The serum phosphorus concentration was low in 2, normal in 5 and high in 1. Surgery was successful in correcting the problem in all cats where surgery was tried (7). None developed clinical signs of hypocalcemia post-operatively although several were hypocalcemia. Six treated cats all had over one year survivals, although one cat had a recurrance after 1.5 years.

Hypocalcemia-Hypoparathyroidism

Hypocalcemia is a less frequently encountered clinical entity than hypercalcemia. However, it can be life threatening when it is caused by hypoparathyroidism. The list of rule-outs for hypocalcemia is long but only a few are clinically important.

Causes of hypocalcemia in clinical practice

(From Ettinger-Textbook of Internal Medicine 4th ed)

- Parathyroid Disorders
  - Primary hypoparathyroidism
    - Glandular destruction-uncommon to rare
      - Immune mediated destruction
      - Surgical extirpation (iatrogenic)
      - Any cervical disease leading to glandular damage
    - Idiopathic atrophy (end stage of autoimmune disease?)
- Chronic renal failure - common
- Hypoalbuminemia (relative hypocalcemia) common
- Acute pancreatitis - common
- Puerperal tetany (eclampsia) common
- Intestinal malabsorption disorders
- Nutritional secondary hyperparathyroidism (rarely hypocalcemic)
- Anticonvulsant therapy - rare
- Acute renal failure - rarely hypocalcemic
- Ethylene glycol toxicity - common
- Phosphate containing enemas - rare
- Miscellaneous causes
  - Laboratory error
  - Use of EDTA-coagulated blood
  - Vitamin D deficiency
  - Transfusion using citrated blood
  - Soft tissue trauma
  - Medullary carcinoma of the thyroid
  - Primary and metastatic bone tumors
  - Cancer chemotherapy

Primary hypoparathyroidism is a naturally occuring disease in which the parathyroid glands decrease or cease secretion of PTH leading to clinically significant hypocalcemia. All the clinical signs are related to the hypocalcemia. As with hyperparathyroidism, the finding of hypocalcemia requires the clinician to determine its cause, as many are not clinically important while others are life-threatening and must be treated aggressively.

Surgical extirpation of the parathyroids: Post-operative hypoparathyroidism is the most common cause for this disorder in animals. This is particularly true in cats who have surgical removal of their thyroids for hyperthyroidism and subsequently develop hypoparathyroidism. Post-operative hypocalcemia

is seen in between 22 and 33% of cats having bilateral thyroidectomies. Clinical signs usually do not develop until the calcium is < 7.0 mg/dl.

Chronic renal failure: Chronic renal failure is one of the most common degenerative diseases in aged dogs and cats. In most animals the phosphorous is elevated and the calcium is normal. However, in chronic renal failure you may see both hypocalcemia (more common) and hypercalcemia (less common). Although this finding is seen with some regularity it is rarely associated with clinical signs. The total calcium is rarely < 8.0 mg/dl in renal failure patients. In addition, the metabolic acidosis accompanying chronic renal failure tends to increase the ionized calcium concentration reducing the chances of tetany developing.

Hypoalbuminemia: In our practice, hypocalcemia is seen more often in hypoalbuminemic patients than for any other cause. The problem is due to decreased albumin binding of calcium that results in a decreased total calcium. Ionized calcium concentrations are normal. It is important to always evaluate the albumin concentration in any patient in which hypocalcemia is noted to be sure it is not "relative" hypocalcemia. The correction factor mentioned in the previous section will allow you to determine if the decreased calcium can be totally explained by the depressed serum albumin concentration (Corrected calcium = measured calcium mg/dl - measured albumin g/dl + 3.5).

Acute Pancreatitis: Hypocalcemia is occasionally observed in animals with pancreatitis and only rarely associated with clinical signs of hypocalcemia. The cause is still debated but it is likely due in part to tieing up of calcium in fatty acid complexes around the gland and partially due to decreases in albumin seen in this disease (relative hypocalcemia).

Eclampsia: Seen in post-parturient, lactating dogs who occasionally develop severe hypocalcemia (< 6.5 mg/dl). Signs are similar to hypoparathyroidism and will be discussed there. The diagnosis is easy as it is obvious the dog or cat is lactating and has signs compatible with hypocalcemia.

Spontaneous primary hypoparathyroidism: This is a relatively rare disease in clinical practice, but since other causes for hypocalcemia are relatively easy to define, it should be considered in any dog or cat in which unexplained severe hypocalcemia is identified. The age range is very wide in dogs, ranging from 6 weeks to 13 years of age (mean 4.8 years). The majority, 2/3, are female. The most common breeds predisposed to hypoparathyroidism are toy poodles, miniature schnauzers, Laborador retrievers, German shepherds, and terriers. Signs are usually abrupt in onset and reflect neurological or neuromuscular findings. Signs may be exacerbated by excitement or

exercise. The duration of illness can be from 24 hours to months before diagnosis.

Clinical signs of hypocalcemia (From Ettinger, 4th edition)
Nervousness
Generalized seizure
Rear leg cramping or pain
Focal muscle fasciculations/twitching
Ataxia, stiff gait
Facial rubbing (intense)
Aggressive behavior
Panting
Weakness
Inappetance
Biting/licking at paws (intense)
Signs are usually acute in onset, animals are usually tense or excited. Facial rubbing/scratching is seen in about 50% of cases but may not be elicited in the history unless asked specifically. Neuromuscular signs such as muscle twitching, generalized tremors and fasciculations or trembling are common. A stiff, rigid gait with an arched back is also common. Seizures are frequent, occurring in 20 to 25% of cases. Animals do not consistently lose consciousness. Often, seizures are actually observed by the veterinarian, an uncommon event with most idiopathic epileptics. Most, but not all, seizures spontaneously abate without treatment. The animals are often tense and reluctant to allow handling, as they have muscle pain when manipulated. Anterior and posterior lenticular cataracts can be seen in 30% of cases. They are usually small, punctate to linear opacities in the anterior and posterior cortical subcapsular region. They are not severe enough to affect vision. Mild fever may be seen in many dogs probably a result of increased muscular activity.

Diagnostic evaluations
In all cases the finding of severe hypocalcemia is a serendipitous observation after a CBC, chemistry profile and urinalysis are evaluated in cases of non-localized neurological signs. The total calcium will consistently be < 6.5 mg/dl. Serum phosphorous concentrations are usually elevated in these animals and generally, no evidence for renal disease is found. The rest of the data base is often normal and other causes for hypocalcemia are not identified. Serum PTH concentrations will be non-detectable or very low in all animals with primary hypoparathyroidism. However, these assays require several days to process and patients must be treated while awaiting results of PTH assays.

Management of Hypocalcemia and Hypocalcemic Tetany

Patients with signs of hypocalcemic tetany require immediate intravenous calcium therapy. Ten per-cent calcium gluconate is given immediately, to effect. The dose is 1.0 to 1.5 ml/kg or 5 to 15 mg/kg given slowly IV over a 10 to 30 minute period. Calcium chloride can be used but it is highly toxic to veins and subcutaneous tissues should it get perivascular. Thus, always use calcium gluconate. Patients are monitored for resolution of their CNS signs and an ECG can help monitor for calcium toxicity. If bradycardia, premature ventricular complexes or shortening of the Q-T interval is seen, the infusion is briefly discontinued. The total dosage is variable and the infusion is generally stopped once clinical signs have abated.

IV calcium gluconate generally will prevent recurrence of signs for 1 to 12 hours. Since oral vitamin-D and calcium generally do not reach peak effects for 24 to 96 hours, some sort of parenteral maintenance calcium support is needed for most patients once the initial "crisis" is managed. You can calculate the dosage of calcium gluconate that was required to stop tetany initally, dilute this volume in an equal volume of isotonic saline and give it every 6 to 8 hours SQ. The serum calcium should be maintained between 8.0 and 9.0 mg/dl with parenteral calcium gluconate. If serum values are below 8.0 mg/dl the dosage is increased and if > 9.0 mg/dl the dosage is lowered.

Maintenance therapy: Primary hypoparathyroidism is treated life-long once it becomes clinically evident. Therapy involves both vitamin-D and calcium initially, however, the calcium supplementation can gradually be withdrawn and only vitamin-D used long-term. Vitamin-D is effective because it promotes intestinal calcium absorption, so supplemental calcium is used initially to be sure adequate substrate is available to elevate the serum level. The long-term goal is to maintain the serum concentration in the low-normal range (8.0 to 9.5 mg/dl) to avoid signs of hypocalcemia, yet also avoid the risk of soft tissue mineralization (nephrocalcinosis) and renal calculi formation, should your therapy raise the calcium and phosphorous too high.

Vitamin D_2 (Ergocalciferol): Vitamin D_2 (40,000 USP units/mg) is widely available, inexpensive and works well in many animals with hypoparathyroidism. Its main disadvantage is its slow onset of action, and slow metabolism if inadvertently overdosed. Initial large dosages, 4000 to 6,000 u/kg/day, SID are given to offset the resistance to the drug and saturate body fat stores. Clinical responses are generally noted in 5 to 14 days after initiating oral therapy. Parenteral calcium suppelmentation can usually be discontinued one to 5 days after beginning oral therapy.

Dogs and cats should be hospitalized during initial treatment, until their serum calcium concentration remains stable between 8.0 and 10 mg/dl. The pet is then discharged and Vitamin-D_2 given every other day. Serum

calcium concentrations are moniored weekly with the vitamin D_2 dose adjusted to maintain the serum conccnetation at 8 to 9.5 mg/dl. 'The aim of therapy is to avoid hypocalcemic tetany, yet the most common problem is inducing iatrogenic hypercalcemia. Once the pet is stable, monthly rechecks are required for 6 months. These should be followed by re-checks every 2 to 3 months forever. Drug induced hypercalcemia can cause severe renal failure that may be irreversible if not identified early and treated aggressively. The frequency of administration of vitamin D can vary from daily to once weekly depending on individual patient variability.

Hypercalcemia induced by vitamin D is difficult to manage because of the long half-life of the drug. It may take 1 to 4 weeks for hypercalcemia to resolve once it is induced. Medical management of the hypercalcemia involves intravenous saline, furosemide and potentially glucocorticoids. Therapy for hypercalcemia is particularly indicated if the calcium x phosphorous product is between 60 and 80.

Dihydrotachysterol (25-OH-cholecalciferol): Dihydrotachysterol is more advantageous than vitamin-D_2 because of its more rapid onset of action (1 to 7 days) and shorter half-life should hypercalcemia develop. It is significantly more expensive than vitamin-D_2, however. Its potency is significantly greater than vitamin D_2 with 1.0 mg of dihydrotachysterol equivalent to 120,000 units of vitamin D_2.

Initial dosages of dihydrotachysterol are 0.03 mg/kg/day for 2 days or until effect is demonstrated, then at 0.02 mg/kg/day for 2 days, and maintenance dosages are 0.01 mg/kg/day. Pets are, again, hospitalized until an effect is noted, and the calcium is maintained between 8.0 and 9.5 mg/dl. Some animals appear to be refractory to the tablet and capsule form but respond well to the liquid form. Rarely, animals fail to respond to any formulation of dihydrotachysterol but respond well to vitamin-D_2 or calcitriol. Rechecks are done weekly initially and then decreased to every 2 to 3 months once serum calcium concentrations appear stabilized.

1,25-Dihydroxyvitamin D_3 (Calcitriol): Calcitriol is the biologically active form of vitamin D and has a more rapid onset of action (1 to 4 days) and more rapid elimination (<1 day) than either of the other two drugs. Recommended dosages for dogs and cats are 0.03 to 0.06 μg/kg/day. The major disadvantages of this drug are its high cost and available forms for humans are generally too large for small dogs and cats.

Calcium supplementation: Numerous oral calcium supplements exist to use in early correction of the hypoparathyroid dog or cat. Generally calcium carbonate is preferred because of its low cost, high percentage of calcium and

ready availability in drug stores in the form of antacids. For cats the dosage of calcium is approximately 0.5 to 1 gm/day, in divided dosages. In dogs, the dosage is usually 1.0 to 4.0 gms/day, in divided dosages. These dosages are approximate only and the primary therapy is adequate dosages of vitamin D in one of its forms.

Prognosis

The prognosis for dogs and cats with spontaneous hypoparathyroidism is generally excellent if appropriate dosages of vitamin D are provided and severe hypercalcemia is avoided. Rechecks at 1 to 3 month intervals once the patient is stable help avoid significant swings in serum calcium that may harm the pet.

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