Review of Vitamin D Metabolism and Diagnostics in Camelids

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Introduction

Abnormal bone growth is a commonly diagnosed problem in young growing animals of all domestic species and is usually related to an array of nutritional deficiencies. A rickets syndrome in juvenile llamas and alpacas characterized by a shifting leg lameness and enlargement of the joints, most noticeably the carpus, has been described.[1,2] Affected crias have variably shown a slowed growth rate, reluctance to move, and kyphosis. Radiographic evidence of physeal ectasia and irregular growth plates were consistent with a diagnosis of rickets. A common clinical pathologic finding of low serum phosphorus concentration (< 3 mg/dl) led to the suggestion of inadequate phosphorus intake being the underlying etiology.

We showed that affected crias were vitamin D deficient and therapeutic administration of vitamin D would correct serum phosphorus concentration and reverse bony changes with clinical recovery.[3] Further research characterized seasonal changes in calcium, phosphorus and vitamin D relative to disease risks,[4] parenteral injections for prevention and treatment (Van Saun, published data),[5] and dietary supplementation requirements (Van Saun, unpublished data). Unfortunately, vitamin D is one of the more toxic essential nutrients. Given the usual adage that if a little is good, a lot is better, the potential for vitamin D intoxication is of concern and needs further study. This presentation will review available data on vitamin D intoxication based on research data and clinical cases in llamas and alpacas.

Vitamin D Metabolism in Camelids

Metabolism of calcium (Ca) and phosphorus (P) is intertwined with vitamin D. Specific actions of the active form of vitamin D (1,25 dihydroxycholecalciferol) are mediated by the presence or absence of the counter-regulatory hormones parathormone (PTH) and calcitonin (CT). There is a dynamic balance between dietary ingestion and absorption of Ca and P from the intestines, resorption or deposition in the bone, recycling of P via the saliva and elimination of Ca and P via the urine, feces and milk. Vitamin D is of central importance in Ca and P metabolism having a direct effect on the rate of intestinal absorption, bone deposition and urinary loss. Of particular importance is the role of vitamin D in stimulating intestinal absorption and decreasing urinary losses of Ca and P. Without sufficient vitamin D activity, intestinal absorption efficiency of dietary P is greatly diminished. Renal excretion of P is a minor regulatory pathway in ruminants compared to the recycling of P in the digestive tract through saliva.[6] Reduced intestinal absorption of P resulting from vitamin D inadequacy would potentially result in greater losses of endogenous P from salivary recycling, thus, inducing a hypophosphatemic condition. The question is whether or not camelids respond similarly to other species in the face of vitamin D toxicity with varying severity of hypercalcemia, or is serum phosphorus concentration more indicative of toxicity? In all our studies supplementing vitamin D either parenterally or orally, serum Ca was minimally influenced by vitamin D status whereas serum P concentration was highly associated with vitamin D status.

Vitamin D Toxicity

I am not aware of any published study characterizing physiologic response to high doses of vitamin D in llamas and alpacas, though we have data from an unpublished study. There is one published case study[7] and information from various clinicians regarding suspected or confirmed cases of vitamin D intoxication of llamas and alpacas.

Following our studies on the pathogenesis of vitamin D deficiency disease and its treatment, we initiated a study to assess the degree of toxicity vitamin D has in the llama and alpaca. Initially 12 llamas and alpacas were assigned to 1 of 4 treatment groups with varying levels of a single vitamin D intramuscular injection (0, 8000, 16000 and 32000 IU/kg BW). These values were based on toxicity studies in other species with 32,000 IU/kg BW

resulting in acute death in dairy cattle.[8] Serum vitamin D concentrations showed a dose-dependent response; however, no clinical evidence of acute vitamin D toxicity was appreciated. Following these results, a single animal was treated with a higher dosage (64,000 IU/kg BW) and again no acute toxicity was observed on clinical or postmortem evaluation. In reviewing these results, serum vitamin D and P concentrations were in the toxic range for most other species, but serum Ca remained within normal limits. The high serum P values are of concern since they may result in a precipitation of Ca and P crystals in blood, urine and body tissues over time. A third trial using 9 llamas at 3 vitamin D treatments was initiated using an emulsified form of vitamin D, as was used in the previous supplementation studies. Again dose-dependent vitamin D responses were observed, but no clinical evidence of acute toxicity. Clinical chemistry panels were completed on all animals and no evidence of renal dysfunction or other abnormalities were evident. Of the animals euthanized, there was evidence of metastatic mineralization of blood vessels in those receiving the higher doses (>8000 IU/kg BW). Long-term toxicity problems were not addressed in this study and need to be of concern given the observed changes in serum P concentrations.

In the published case study, crias were intoxicated with oral vitamin D at doses of 3750 IU/kg/day and 12,987 IU/kg/day for 7 and 5 days, respectively.[7] These crias presented with both hyperphosphatemia and hypercalcemia and had azotemia with nephrocalcinosis identified on necropsy. In comparing the two different studies, response to vitamin D intoxication may depend upon dosing method, duration and age of the animal.

Diagnostic Evaluation

Concentration of 25-hydroxycholecalciferol (25VitD) in serum is the standard for assessing nutritive status relative to vitamin D. The challenge here is having appropriate reference ranges for interpreting the values (Table 1).[9] The two vitamin D intoxicated crias of the case study had serum 25VitD exceeding 600 nmol/L.[7]

Table 1. Age-Based Criteria for Serum Vitamin D (25-Hydroxycholecalciferol) Concentrations in Llamas and Alpacas

Age Category	Months of Age	Units	Mean	Stand. Dev.	Median	Expected Range
Cria	1–6	nmol/L	136.4	116	76.0	26–344
		ng/mL	54.6	46.4	30.4	10.4–137.6
Weanling (Tuis)	7–12	nmol/L	85.2	58.3	73.0	28–316
		ng/mL	34.1	23.3	29.2	11.2–126.4
Yearling	13–24	nmol/L	112.7	80.4	81.0	40–359
		ng/mL	45.1	32.2	32.4	16–143.6
Adult	>24	nmol/L	119.2	91	91.0	30–414
		ng/mL	47.7	36.4	36.4	12–165.6

ng/mL, nanogram per milliliter; *nmol/L*, nanomole per liter.
Note: Concentrations below 25 nmol/L (10 ng/mL) or above 500 nmol/L (200 ng/mL) are consistent with deficiency and toxicity disease risks, respectively.

Serum vitamin D concentrations are expensive and often not available in a timely fashion. Animals may be exposed or at risk for vitamin D intoxication, yet may have normal renal function. Elevations in serum Ca or P concentrations may not be sufficient to adequately diagnose risk from vitamin D intoxication. With the uncertainty in using either hypercalcemia or hyperphosphatemia as a diagnostic indicator, another possibility is using the product of Ca and P concentrations as a measure of risk for metastatic calcification. The calcium x

phosphorus (CaP) concentration product (mg^2/dl^2) has been used in human medicine as an indicator for risk of renal mineralization. A threshold of 55 mg^2/dl^2 has been used, but its applicability to camelids needs to be validated.

Using multiple collections of serum Ca and P concentrations (n=1189) from survey and vitamin D administration studies, CaP product values were evaluated. Overall CaP product was highly associated (r^2=0.37; P<.0001) with vitamin D status. Age group was not significant, but there was a significant interaction between CaP product and Age group (P=.0002). Healthy, non-vitamin D treated adult camelids had a CaP of 48.1 ± 3.1 mg^2/dl^2. Age influences this parameter with yearlings (75.9 ± 5.1 mg^2/dl^2) and crias (95.3 ± 3.2 mg^2/dl^2) having higher values. Association between CaP product and vitamin D was stronger for higher vitamin D concentration than for low vitamin D, though these preliminary data would suggest CaP product could be a proxy for diagnosing vitamin D deficiency. This parameter was used to evaluate potential vitamin D intoxication in an alpaca herd exposed to a high dietary vitamin D (191,000 IU/lb) supplement over a period of months. The percent of adult samples having a CaP greater than or equal to 60 mg^2/dl^2 was significantly higher in samples from vitamin D injected camelids (43.8%) and the samples collected from the vitamin D supplement exposed camelids (31.9%) compared to camelids not supplemented with vitamin D (16.2%). The two vitamin D intoxicated crias from the case study presented with CaP products of 194.6 and 155 mg^2/dl^2; values much higher than non-exposed crias.[7]

Clinical Presentation and Treatment

Vitamin D intoxication results in non-specific clinical signs of anorexia, weight loss, lethargy, depression and renal dysfunction. Additionally cardiac arrhythmias or lameness may be present. One challenge here is that many of these signs are often associated with problems of vitamin D deficiency and often a first response in young camelids is to administer parenteral vitamin D. Additional clinical signs associated with cardiac, renal or respiratory function may be present depending upon the degree of soft tissue mineralization.

There is no therapeutic correction for vitamin D intoxication. One should remove the source of vitamin D and provide supportive care to ensure hydration and renal function. Dietary content of calcium and phosphorus should be minimized to reduce available mineral for absorption. Intensity of supportive care will depend upon the severity of renal dysfunction.

Summary and Conclusions

Llamas and alpacas seemingly are seemingly tolerant of acute vitamin D toxicity. However evidence is present that higher doses of vitamin D may result in altered P metabolism with the possibility of Ca and P precipitation in urine and tissues. Vitamin D supplementation should be approached carefully and under the guidance of a veterinarian. Increasing the suggested treatment dosage of vitamin D is not recommended as there is no evidence of improved effect and suggestions of deleterious effects to animal health are evident.

References:

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