PROCEEDINGS OF THE

NORTH AMERICAN VETERINARY CONFERENCE

VOLUME 20

JANUARY 7-11, 2006

ORLANDO, FLORIDA

SMALL ANIMAL EDITION

CALCIUM METABOLISM IN RABBITS: WHAT'S NEW?

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The two most vexing problems in rabbit medicine are the pathologic consequences of calcium metabolism and dental disease. Perhaps the two are related but this discussion focuses primarily on calcium metabolism in rabbits. A more appropriate title possibly should be "Calcium metabolism in rabbits: What's old?" Some of the preconceived notions of calcium metabolism in rabbits deserve a second look and, sometimes, a first look.

One of the more commonly held thoughts on calcium metabolism in rabbits is that the rabbit's gastrointestinal system is designed to absorb all the dietary calcium that is presented to it. In other words, the more calcium in the food, the more calcium enters the gastrointestinal tract. Eventually, the theory goes, excess calcium the body cannot use stays in the blood stream and is excreted through the urinary tract. This theory postulates that there does not exist in rabbits the delicate balancing act between calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) found in all other mammals. Without this ballet act between these four components, there is no gateway to prevent an overabundance of calcium absorption through the gastrointestinal tract. It is also thought that the great majority of calcium absorbed by the gastrointestinal tract leaves the body through the urinary tract. This differs from almost all other mammals as studies show that in most animals other than rabbits, calcium is excreted, harmlessly, through fecal material. The fact that large amounts of excess absorbed calcium are passing through the renal system is what some believe is the cause of urinary calcium disorders. Many have taken all of these ideas as fact, without reading the original studies. All of this has led to the prevalent theory that to decrease calcium absorption and prevent renal calcium diseases, rabbits should be fed a diet that is as low in calcium as possible but not too low to cause hypocalcemia-associated-disease. This has led to an entire industry creating diets based on the lowest calcium concentrations in their feeds. Foods prepared from timothy hay instead of alfalfa hay are universally recommended, and low calcium treats are highly recommended.

To best understand calcium metabolism in rabbits, it is important to review the basics of calcium metabolism in mammals. In most mammals, plasma calcium normally circulates within a narrow concentration range of 8.5 to 10.5 mg/dL. In rabbits, the normal range, depending on the methodology, is between 12.5 and 16 mg/dL. Maintenance of this concentration requires the coordinated activity of the kidneys, the intestine, and the skeleton. The extracellular fluid (ECF) concentration of calcium is tightly maintained within a rather narrow range because of the importance of the calcium ion to numerous cellular functions including cell division, cell adhesion and plasma membrane integrity, protein secretion, muscle contraction, neuronal excitability, glycogen metabolism, and coagulation. This is true in all mammals, including rabbits. Therefore, it would seem unlikely that plasma calcium in rabbits is artificially elevated due to diet as the ECF concentration needs to be so tightly maintained. Primary hormonal regulation of this system is carried out by PTH, a product of the parathyroid glands. The physiologic role of PTH is to support the plasma calcium concentration. When plasma-ionized calcium activity falls, PTH secretion increases and results in more efficient renal calcium reabsorption. If reductions in calcium are sustained, PTH stimulates renal production of 1,25 dihydroxyvitamin D (calcitriol), the active metabolite of vitamin D, which promotes intestinal calcium and phosphorus absorption. When decreases in calcium activity are severe or prolonged, hypersecretion of PTH leads to activation of bone remodeling and support of ECF calcium at the expense of the skeleton.

As noted previously, rabbits have a plasma calcium concentration that is elevated compared with other mammals. It has been postulated this is due to the calcium-rich diet fed to pet rabbits. Anecdotally, no one has reported a lowering of blood calcium by feeding a diet low in calcium to pet rabbits. In fact, research in the last 15 years is beginning to change the idea of diet manipulation as a means to lower blood calcium. Studies related to gene mapping in people, rabbits, and rodents have shown results that shed light on rabbit calcium concentration. According to Warren et al (1989), in rabbits, hypercalcemia (relative to human) is normally present and associated with an elevated set point for Ca^{2+}-regulated PTH release. These researchers have found that it takes a higher concentration of blood calcium in rabbits to turn off the production of PTH. Rabbits require a higher calcium concentration to discontinue PTH production. When PTH is no longer produced, the GIT absorption of calcium is halted, the renal reabsorption of calcium stops, and the release of calcium from the skeleton is arrested. In support of this statement, wild members of the pet rabbit species, *Oryctalgus cuniculus*, also have relatively elevated calcium concentrations as opposed to other mammals.

Early research in the 1960s is often quoted. These papers seem to show that as dietary calcium is increased in the diet, blood calcium increases. These studies were done on very young growing rabbits. Also, there were many variables not controlled for. Most importantly, these studies lack much of the information needed to decide whether the blood calcium results that were obtained are both accurate and precise. When calcium is measured in dietary experiments, it is important to look at the relationship of calcium to phosphorus. This important ratio may be responsible for experimental results that have guided dietary recommendations for the last 30 years of pet rabbit medicine.

The question is, can we lower the blood calcium in rabbits? And if it can be lowered, will this decrease the morbidity and mortality associated with calcium disorders in rabbits? It is unlikely that the blood calcium in rabbits can be lowered due to the fact that the high concentration of calcium may be physiologically normal in rabbits. Therefore, the question is, can we prevent the detrimental effects of calcium metabolism in rabbits? There may be only a few ways to do this. First, it is important to make sure the rabbit does not absorb any more calcium than is necessary. Advise owners not to give supplements to the food. Vitamin and mineral supplements should be avoided. Keep vitamin D concentrations in the normal range; do not supplement vitamin D in rabbits.

Drugs can be used to lower calcium in the plasma; these drugs are used in humans with various diseases and for various purposes. Since lowering the dietary calcium may not lower the blood calcium, other methods may be necessary to lower plasma calcium concentrations in severe cases. Biphosphonates and calcimimetic agents (those that mimic or potentiate the action of calcium) are used in people where there is accelerated bone resorption. Bone resorption is an important factor in the pathogenesis of hypercalcemia in people. Bisphosphonate is one treatment of choice for inhibition of bone resorption. These agents can have severe side affects and may cause transient fevers, flu-like symptoms, or myalgias for a day or two and transient hypocalcemia and/or hypophosphatemia may result. Without research, these agents are not yet acceptable for rabbits with calcium metabolism effects.

Is there a way to prevent rabbits from calcium metabolism disorders? It may not be possible. As mentioned, diet should be scrutinized to be certain no added calcium or added vitamin D are in the diet. Drugs can be used to manipulate the blood calcium concentration but there are side effects to these drugs that have not yet been tested in rabbits. It may be that once rabbits reach a certain age, it is inevitable that calcium metabolism may cause disorders of the urinary tract.

Recommended Reading

1. Goltzman D. Discoveries, drugs and skeletal disorders. Nat Rev Drug Discov 2002;1:784-796.
2. Marcus R. Disorders of calcium concentration. Best Practice of Medicine. 2002.
3. Warren HB, Lausen NCC, Segre GV, El-Hajj G, Brown EM. Regulation of calciotropic hormones in vivo in the New Zealand White rabbit. Endocrinology 1989;125:2683–2690.