

Dr Geoffrey Smith, Assistant Professor of Ruminant Medicine at North Carolina State University

■ Bioavailability and Pharmacokinetics of Oral Omeprazole in Camelids

“T

hat job is going to give me an ulcer!”

Who hasn't made such an outcry or, at the very least, heard co-workers or family members express frustration and anxiety coupled with concern over the health of their digestive system?



Dr. Geoffrey Smith

Aside from emotional stress, an organism called *Helibacter pylori* is responsible for peptic ulcers in people. This bacteria has also been isolated from domestic cats. According to Dr. Geoffrey Smith, Assistant Professor of Ruminant Medicine at North Carolina State University, *Helibacter pylori* is not an issue whenever stomach ulcers are diagnosed in large animals.

In the proposal he submitted to Morris Animal Foundation (MAF), Dr. Smith cited research published by Murray E. Fowler, DVM (as well as Brad Smith, DVM, et al.) to make a compelling argument for the significance of his own study: “Third compartment (stomach) ulcers are a common cause of morbidity and mortality in camelids of all ages. Although the exact cause and pathogenesis of stomach ulceration in these animals is not completely understood, stress appears to be the most common predisposing factor” (Dr. Geoffrey Smith, MAF Proposal, *Bioavailability and Pharmacokinetics of Oral Omeprazole in Camelids*).

Before MAF approves funding for a project, the Principal Investigator must present clearly-defined objectives to be accomplished. Dr. Smith's main goal was to examine the bioavailability of orally

administered Omeprazole (GastroGard) in camelids. Additionally, he hoped to determine the optimal dose necessary to successfully treat and/or prevent stomach ulcers in llamas and alpacas. Once approved, the project was co-sponsored by the Alpaca Research Foundation (www.alpacaresearch-foundation.org).

When I contacted Dr. Smith in early August of 2005, he had already completed his research and was prepared to share the somewhat surprising results.

Prior to our pre-arranged phone interview, I consulted *The Merck Veterinary Manual* (8th Edition) to refresh my memory on the issues concerning gastric ulcers in farm animals. It makes for disturbing reading. The authors discuss GI ulceration as a “common problem in small and large animals,” including camelids. Gastric ulcers pose a health threat to a significant number of foals and pigs, with cases of abomasal ulcers “increasing in importance” in mature cattle and calves. Why do so many agricultural animals suffer from ulcers? What causes their illness? What contributes to it?

Causes of Ulcers

The first question I asked Dr. Smith was, “Do you believe that stress is the cause of gastric ulcers?” “Yes, I do,” he replied without hesitation. “I don't think it's the only reason, but in my opinion, environmental stresses play a large role. That's why I encourage my camelid clients at North Carolina State University to send a patient with a buddy.”



The Alpaca Research Foundation (ARF), in conjunction with Morris Animal Foundation (MAF) and other groups in the llama and alpaca communities, provides funding grants to veterinarians and scientists engaged in research that has the potential to improve the health and well-being of our animals. *Alpacas Magazine* is pleased to bring you another in a series of interviews with the researchers carrying on this important work.

“Yes, many alpacas panic when owners remove them from their herdmates,” I agreed. “Exactly,” Dr. Smith continued, “it’s not unusual for sick animals to be hospitalized and develop other, unrelated symptoms such as an ulcer due to stress.” He added, “I also emphasize that camelid owners should keep llamas and alpacas in pairs at their farms, never as singletons.”

“What about diet?” I broadened my inquiry. “In cows, a high grain diet can cause ulcers,” Dr. Smith explained. “Corn and wheat are among the main culprits as being the grains hardest to digest. Oats are easier on the digestive system. Also, it’s important that grains or other supplements are fed as coarsely textured as possible.”

Breeders and owners of other livestock species are well aware of diseases caused by nutritional programs rich in concentrates and low in forage. *The Merck Veterinary Manual* lists, among others: feedlot bloat, displaced abomasum, lactic acid acidosis, founder, laminitis, and enterotoxemia. “There is certainly no harm in feeding small amounts of grain or pelleted feed to alpacas,” Dr. Smith stated and admitted to rewarding the llamas in his research study with a handful of treats after an examination. “However, the bulk of a grazing animal’s diet should be excellent pasture and quality hay,” he insisted firmly.

In horses, the incidence of gastric ulcers is so high (up to 88% of all Thoroughbreds according to *The Merck Veterinary Manual*), it’s no wonder that GastroGard, the paste form of Omeprazole, was initially developed to treat equines. “Some veterinarians even advise horse owners to use GastroGard prophylactically, that’s how prevalent the problem is,” Dr. Smith mentioned.

Although reducing stress and providing a good diet go a long way to prevent ulcers, such a care protocol is obviously of no immediate help if disease is already present. Dr. Smith’s research is therefore of utmost importance to camelid owners and breeders. GastroGard works very well in horses, and the caretaker can easily medicate the animal without assistance. Dr. Smith hoped that the product would have the same beneficial effect on camelids. Six healthy llamas were brought to North Carolina State University on loan from the Southeast Llama Rescue program to determine what



concentration of the drug would accumulate in their bodies.

One nice aspect of Dr. Smith’s research was the fact that it was not necessary to induce disease. Six healthy llamas arrived, remained healthy, and were returned, none the worse for wear, to their rescue organization at the conclusion of the project.

Dissapointing Results

The outcome of the clinical trials was disappointing. “The drug was poorly absorbed,” Dr. Smith explained. “Bioavailability was only 2% of the dose. The first stomach compartment (C-1) in camelids is full of bacteria. It is possible that this bacteria degraded the drug before it had a chance to be absorbed into the bloodstream. Typically, you’ll get gastric ulcers in camelids in the third compartment. We even doubled, then tripled the dose normally used on horses – it didn’t make a difference.” It was easy to tell that Dr. Smith had hoped to present Morris Animal Foundation, ARF, and their supporters with more positive results.

“Why does GastroGard have to be absorbed into the bloodstream? Can’t the drug simply travel through the digestive system and eventually reach C-3?” I asked.

“Omeprazole is a proton-pump inhibitor,” Dr. Smith explained patiently. “It *has* to be absorbed into the blood to work. If it isn’t, there is no way I can think of that it would still be effective. I know that anecdotal evidence suggests otherwise. Some veterinarians and owners may not believe the results of my research,” he speculated. “Where do we go

Alpacas are herd animals – keeping them with at least one buddy, especially when traveling, or if they have to go to the vet, will help reduce stress.

ARF Investigator Profile

The bulk of a grazing animal's diet should come from good pasture and quality hay.



from here?" I asked. "Well, the injectable version of Omeprazole certainly works when given intravenously. It's just not as convenient and cost effective for owners," Dr. Smith replied. He explained how he inserts a catheter into an alpaca patient's jugular vein to administer the drug. "Although my research did not support the belief that GastroGard will work in alpacas, there is no reason to give up on its use completely. A future study could also monitor stomach pH," he suggested.

With a smile, I remembered the conversation I had had with a young family friend, an avid swimmer. When I explained the basic facts of stomach pH to her, she had laughed out loud. "Then mammals' stomachs are like the water in a swimming pool. Their pH has to be just right or they can't be completely healthy." Her off-beat analogy proved to me that she had grasped the fundamental concept of a functional digestive system.

Although camelids are not true ruminants (some scientists refer to them as "modified-" or "pseudo-" ruminants), their three stomach compartments are nevertheless a complicated structure. They are labeled C-1, C-2, and C-3. The glands that secrete digestive enzymes and acid are located in what is called the terminal one-fifth of C-3. A healthy pH

level varies from 6.4-7.0 in the three compartments, dropping to 2.0-3.0 in the terminal one-fifth of the third compartment. Any time this delicate pH balance is disturbed, the normally very efficient camelid digestive system fails to function properly. Acute indigestion develops when the pH level drops considerably due to, for example, the consumption of a large quantity of concentrates. A chronic overproduction of stomach acid may very well result in a gastric ulcer. That's why GastroGard, which causes a prolonged (24 hours) inhibition of gastric acid production, is so effective in healing ulcers in horses.

In alpacas and llamas, however, the challenge is to get the paste moved well past the bacteria that degrades the drug in C-1 and into C-3 where ulceration takes place. How can that be accomplished without surgery or other invasive procedures?

Other Possibilities

"There is a possibility we can explore," noted Dr. Smith, "and it involves a digestive mechanism typical for ruminants called the esophageal groove reflex." I had read about this fascinating phenomena in *The Merck Veterinary Manual* not too long ago. This reflex causes digestive passageways to close while the ruminant neonate suckles from its dam or

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a bottle. The milk is thus channeled into the appropriate compartment for proper digestion. In camelids, if the reflex functions properly, it ensures that colostrum and milk are funneled into the C-3 compartment. Deposited in C-1, milk ferments and causes severe digestive problems. This is a good reason not to encourage neonate camelids to drink from buckets. In calves, “ruminal drinkers” often develop diarrhea and are generally unthrifty.

Dr. Fowler, the author of *Medicine and Surgery of South American Camelids*, tells readers that “the esophageal groove of the camelid is not as well developed as in true ruminants. There is only a single lip, as contrasted with two in the ruminant.” He cautions caretakers of orphaned neonates to insert a feeding tube only as far as the thoracic inlet instead of directly into the stomach. “Fluid traversing the thoracic esophagus may cause reflex closure of the esophageal groove and shunting of the colostrum to C-3 of the stomach, where it belongs” (Fowler).

As crias become older and stop nursing, the need for the esophageal groove reflex to work diminishes. Eventually, it ceases to function. If you are trying to prevent medication from being degraded in C-1 and wish to channel it directly into C-3, Dr. Smith suggested a medical “trick” used in ruminants. “The appropriate salt solution, administered orally, may achieve closure of the groove,” Dr. Smith explained. “We could certainly explore this type of treatment when administering GastroGard to alpacas and llamas. I have used the procedure in cattle, although not in a controlled study,” he shared with me. Again, *The Merck Veterinary Manual* provided interesting details. For example, it lists a mixture of 2 oz. (60 ml) of 5% copper sulfate, 5% zinc sulfate, and 10% of sodium bicarbonate as being effective in closing the groove in cattle. “Onset of the reflex responses takes 5-10 sec., and the groove may remain closed for up to 60 sec.” (Merck).

I firmly believe that every “closed door” in life leads to the exploration of alternative, and often more exciting, opportunities. Dr. Smith seemed to share that philosophy. The results of his initial research may be disappointing, but they point in a direction that ultimately will be of a much greater benefit to camelids and their owners. Meantime, I believe that it behooves veterinarians, owners, and

breeders to jointly develop a care protocol that helps *prevent* the development of gastric ulcers.

Omeprazole, like any other drug, is not without its side effects. *The Merck Veterinary Manual* warns that it is “contraindicated for chronic therapy”, citing the fact that it is “a microsomal enzyme inhibitor” and that, in man, adverse effects from suppression of gastric acid secretion include development of carcinoids. Although extrapolation from human applications is not always appropriate for other species and may not be in this case, camelid owners are well advised to approach *any* use of drugs with caution.

Throughout the interview, I sensed Dr. Smith’s deep concern for the animals used in his study. It quickly became obvious to me that he thought of the llamas as individuals with physical as well as emotional needs, not merely objects to be manipulated for his research purposes. The members of the Southeast Llama Rescue program who approved the use of their llamas for this project can be well pleased with their decision.

“Where, when, and why did you develop an interest in veterinary medicine?” I finally asked. Dr. Smith shared with me that his parents are college professors. A neighbor next to their home in South Carolina raised pigs, and young Geoffrey was soon “hooked”. His interest later switched from swine to dairy cows. “I have always been especially interested in working with small family farms,” Dr. Smith related. This certainly makes him ideally suited to work in camelid medicine. His camelid caseload at North Carolina State University is small but growing.

Dr. Smith is married to a veterinarian who specializes in small animals. He enjoys spending his free time with his wife and two young children. An English Pointer named Yogi rounds out the family. Introducing such a caring professional to the greater camelid family was a pleasure and a privilege.

Ingrid Wood has been breeding and boarding huacaya alpacas on her Stormwind Farm in New Jersey since 1997. She is an active partner in Alpaca Heritage Events, and is the author of *A Breeder’s Guide to Genetics – Relax, It’s Not Rocket Science*. For other articles please visit www.StormwindAlpacas.com