Research Subject Information and Consent Form

Title of Study: A Proposed New Feline Treatment for Dissolving Thromboembolisms Caused by Hypertrophic Cardiomyopathy

Study Investigator: Michelle M. Raiszadeh, Ph.D.

You are invited to participate in a research study designed to determine the effectiveness of a new treatment for blood clots in cats with hypertrophic cardiomyopathy. The new treatment to be studied involves a naturally occurring enzyme that has been found to have thrombolytic or clot-dissolving abilities. Participation in this study is completely voluntary. You are invited because your cat has been diagnosed with hypertrophic cardiomyopathy resulting in aortic thromboembolism. All cats in this study will be treated with this newly introduced thrombolytic agent, regardless of how long the thromboembolism has been present. If you agree to participate, your cat must not receive any anticoagulant or blood thinning medications. This is because the enzyme used in this study also works as a natural blood thinning agent or anticoagulant and any additional blood thinners administered to your cat may enhance the risk of bleeding when combined with the agent used in this treatment. There are no other known risks related to this treatment. The study investigator has thus far successfully treated 44 cats and observed no adverse effects from this treatment.

WHAT IS THE PURPOSE OF THIS STUDY?
The purpose of this study is to objectively evaluate and further substantiate the efficacy of this newly introduced thrombolytic agent in dissolving blood clots in cats with HCM. This study will accurately determine average dose and time necessary for the enzyme to effectively dissolve clots and allow circulation to return to affected areas of the body.

WHAT WILL MY PARTICIPATION INVOLVE?
If you decide to participate in this research study, it will be your responsibility to orally administer this new thrombolytic agent in tablet form to your cat. The duration of this treatment is expected to last no more than 1 week since the blood clot is expected to be dissolved by this time and circulation is expected to return to affected limbs. This enzyme has the potential to dissolve clots in as little as 30 minutes but time necessary for the clot to be dissolved by the enzyme and circulation to return will depend on the size of the clot and elapsed time since the thromboembolism occurred. For cases in which the thromboembolism occurred a week or more prior to this treatment, a longer treatment time may be necessary. The tablet should be given to your cat every 15 minutes on the first day of treatment and if circulation has yet to return, continue to administer the thrombolytic agent every 15 minutes. Do not exceed 30 tablets in a 24-hour period. A dissolved blood clot will be determined through signs of returned blood flow to the affected areas. These signs include increased temperature, coloration, mobility, and coordination in the cat’s limbs.
ARE THERE ANY RISKS?
There have been no adverse reactions in human, rat, and dog studies that involved this enzyme. However, you are not to administer any other blood thinning agents during this treatment since additional blood thinners can enhance the risk of bleeding.

ARE THERE ANY BENEFITS?
Your cat will receive any benefit obtainable from this treatment, including returned blood flow to affected limbs, improved coordination, pain relief, and other benefits by directly participating in this study. Your participation in this study will provide reproducible results that will benefit other HCM cats in the future by helping us learn how thromboembolisms can be effectively treated.

ARE THERE ANY COSTS?
You will be responsible for purchasing the enzyme in supplement form, but this is the only cost associated with this study. The cost of the enzyme in supplement form will vary from $20 to $40 depending on the supplier and availability but usually the cost averages $25 per treatment.

ARE THERE ANY ALTERNATIVES?
Streptokinase and tissue-plasminogen activator are two drugs available that have the potential to dissolve a thrombus but the risk of reperfusion injury, hemorrhage, the significant cost of the drugs, and the lack of evidence of improved outcome in cats treated with these thrombolytic agents makes their use questionable. The newly introduced thrombolytic agent in this research study has the potential to be safe, effective, and affordable. It is the only thrombolytic agent that can be administered orally. It is not yet veterinary approved but is available as an over-the-counter human supplement.

IF I DECIDE TO START THE STUDY, CAN I CHANGE MY MIND?
Your decision to participate in this research is entirely voluntary. You may choose not to participate. If you do decide to participate, you may change your mind at any time and withdraw from further participation in the study. You will be told of any new and significant findings of the study, as the data is analyzed at periodic intervals, which may affect your willingness to continue.

WILL MY CONFIDENTIALITY BE PROTECTED?
Researchers for this study might use information learned from this research in scientific journal articles or in presentations. None of this information will identify you personally.

WHAT IF I HAVE QUESTIONS?
If you have any questions about this research, please contact the study investigator, Dr. Michelle Raiszadeh, Ph.D. at (703) 408-0175.
Authorization to participate in the research study:

I have read the information in this consent form, reviewed any questions, and I voluntarily agree to participate in this study. I have received a copy of this consent form.

__________________________________________ __________________
Signature of owner or agent for cat Date
Background: Feline hypertrophic cardiomyopathy (HCM) is the most common heart disease in cats. In this condition, the walls of the left ventricle, the heart chamber responsible for pumping blood out through the aorta, become progressively thicker. This causes the chamber size to become reduced, and the ventricle to become stiffer and less compliant, affecting the chamber’s ability to fill with blood. This ultimately affects the heart’s ability to function normally. As a result, cats with HCM have a guarded prognosis. There are several potential outcomes for cats with HCM. Many cats respond well to medical therapy and remain symptom-free for years. Some cats develop fatal heart arrhythmias and die suddenly. In some cats, the disease progresses steadily, ultimately leading to congestive heart failure. A significant number of cats with HCM develop aortic thromboembolism. This is one of the most serious complications associated with hypertrophic cardiomyopathy (HCM), and is one of the most common causes of hind limb paralysis in felines. While there is no cure for HCM, early detection and regular echocardiograms are key to trying to ward off life-threatening problems. Early signs may include a murmur or even heart failure. Unfortunately, death may occur without any other signs present, making the disease a difficult and often deadly one. While medication is commonly given to cats with HCM that have no clinical signs, no medication has been shown to be helpful at this stage and it has been shown that an ACE inhibitor is not beneficial until heart failure is present (at which time a diuretic is most beneficial). Diltiazem generally produces no demonstrable benefit. Atenolol is commonly administered when systolic anterior motion of the mitral valve is present. Thromboembolic disease (TED) is relatively common in Feline HCM. It is thought that ischemic damage to the hypertrophied left ventricular myocardium facilitates thrombus formation and subsequent embolism. Classically the embolus lodges at the iliac bifurcation of the aorta, occluding either one or both of the common iliac arteries. Clinically this presents as a cat with complete loss of function in one or both hindlimbs. The hindlimbs are cold, and the cat is in considerable pain. This pain derives from the exaggerated inflammatory response to the embolus at the point of impact, and the inflammatory mediators released generally have a vasoconstrictor effect further exacerbating the problem. Emboli may, rarely, lodge in other locations, typically the renal or ovarian/testicular arteries as they exit the abdominal aorta. Treatment of TED is variable - typically very low doses of aspirin may be prescribed (aspirin however is extremely toxic to cats and should only be prescribed and administered by a veterinary surgeon). Plavix is also another widely used drug that may or may not prevent clot formation in HCM cats. Thrombolytic agents (e.g., tissue plasminogen activators) have been used, but their cost is usually prohibitively high in veterinary medicine. Despite the relative efficacy of treatment, the prognosis for cats with TED is poor as they are likely to have significant HCM already, and a recurrent bout of TED is very likely. For this reason euthanasia is often considered in TED cats. There are drugs available that have the potential to dissolve a thrombus or embolus. Whether these drugs offer any real benefit remains controversial. The two drugs most commonly used are tissue-plasminogen activator (tPA) and streptokinase. TPA is a protein. It is very expensive with one 50 mg vial costing over $1000. Studies using this drug in cats are scarce. In one study, about two-thirds of cats given this drug had perfusion restored to their limbs. Streptokinase is less expensive. A study of 46 cats with ATE (aortic thromboembolism) that were treated with streptokinase showed about half of the cats had their pulses restored, and 30% had motor function returned to their limbs within 24 hours. The side effects of treating cats with streptokinase or tPA make their use questionable. When cats are treated with these agents, they become susceptible to “reperfusion injury” as blood flow is suddenly restored to the limbs. Electrolyte disturbances such as hyperkalemia (excessively high potassium levels) and metabolic acidosis can result, with direct consequences. In one report of using tPA to treat cats with ATE, 70% of fatal complications were due to metabolic acidosis and hyperkalemia. Hemorrhage can be another adverse side effect, since these drugs are designed to dissolve clots. These drugs must also be administered within 2 hours to be effective.
The risk of reperfusion injury, hemorrhage, the significant cost of the drugs, and the lack of evidence of improved outcome in cats treated with thrombolytic agents makes their use questionable, and many practitioners remain reluctant to administer this form of therapy. The thrombolytic agent that will be used in this study is a naturally occurring enzyme that has been shown to be safe, effective, and affordable. This will be the first official study where this enzyme will be used for the purpose of treating thromboembolisms in cats.