EFFECTS OF ATENOLOL VERSUS DILTIAZEM ON LV DIASTOLIC FUNCTION IN CATS WITH OCCULT HCM*

Karsten E Schober, Dr med vet, PhD, DECVIM
John D Bonagura, DVM, DACVIM; Virginia Luis Fuentes, MRCVS, DACVIM
Columbus, OH

Annual Forum of the ACVIM, Seattle, June 2007

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common acquired cardiac disease of the cat, with unique pathophysiologic characteristics and a great diversity of morphologic, functional, and clinical features. Idiopathic left ventricular (LV) hypertrophy, myofiber disarray, myocardial fibrosis, and abnormal coronary microvasculature causing ischemia; impaired LV diastolic function and asynchrony of LV contraction and relaxation, LV outflow tract obstruction, and left atrial (LA) enlargement and dysfunction; and diastolic heart failure, syncope, sudden cardiac death (SCD), and arterial thromboembolism (ATE) are characteristics of HCM. From a clinical and therapeutic perspective, the distinction between HCM with (HOCM) and without obstruction seems to be important. Also, age of the animal at diagnosis, pattern and magnitude of LV hypertrophy, LA size and LA content, and functional stage of the disease may influence treatment decisions and prognostication.

MANAGEMENT OF HYPERTRPHIC Cardiomyopathy

As in people, HCM in cats is most likely a genetic disease. Therefore, treatment aims at only symptom relief. Clinical signs appear to be caused in large measure by diastolic dysfunction with impaired filling due to abnormal relaxation and increased chamber stiffness, leading in turn to elevated LA and LV end-diastolic pressures (with reduced stroke volume and cardiac output). In human HCM, surgical, interventional, and pharmacological treatment options exist although the majority of patients (95%) are treated only pharmacologically. Septal reduction therapy (surgical myectomy, catheter-induced septal alcohol ablation), mitral valvuloplasty (plication), asynchronous dual-chamber pacing, implantable cardioverter-defibrillator devices to prevent SCD in high-risk patients, cardiac transplantation, and drugs such as beta adrenergic blockers, calcium channel antagonists, disopyramide, amiodarone, sotalol, diuretics, ACE inhibitors, angiotensin-II receptor antagonists, and antiaggregants have all been used depending on clinical signs, severity of the disease, complications, and the genetic predisposition to SCD. Management of feline HCM is limited to only drug treatment. In cats as well as in people, patient response to drugs is highly variable, and the selection of medications has not yet achieved widespread standardization and has been dependent, in part, on the experiences and preferences of individual investigators and centers. This is most likely true in cats with occult or pre-symptomatic HCM and has been subject to debate for many years.

In asymptomatic cats, most clinicians favor the use of beta-blockers, in particular if dynamic obstruction of the LV outflow tract is present. In non-obstructive cats some prefer diltiazem. There is, however, a critical lack of hard data supporting either approach, and the efficacy of empiric prophylactic treatment of HCM in cats has not yet been tested prospectively. There is anecdotal evidence that both atenolol as well as diltiazem may improve clinical signs in a subset of cats with asymptomatic HCM, and there is also evidence that atenolol may relieve the outflow tract obstruction found in cats with HOCM. However, there is no data to confirm the contention that either treatment improves LV diastolic dysfunction (a pathophysiologic hallmark of the disease), reduces ventricular arrhythmias commonly associated with HCM, prevents disease progression and SCD, or prolongs survival. In contrast, there is some concern raised from results in human studies that chronic beta blockade may cause inappropriate bradycardia reducing exercise tolerance and increasing LA size, and may also cause worsening of LA function leading to blood stasis, reduction of LV filling, and the development LA thrombi. A further element of uncertainty with regard to early pharmacologic treatment of feline HCM is the growing awareness that an important proportion of cats with HCM remain asymptomatic for many years and often have almost normal longevity, whether treated or not. Therefore, treatments aiming at preventing or slowing the progression of the disease do not appear to be justified in most asymptomatic cats. Also, although sophisticated echocardiographic techniques now allow for earlier detection of HCM, sensitive and specific biomarker assays for the analysis of circulating cardiac troponin I or feline BNP are commercially available, and genetic testing for one causative disease mutation in the Maine Coon cat is possible in even routine practice, the reliable diagnosis of HCM and in particular in “silent” mutation carriers without evidence of overt LV hypertrophy on the echocardiogram remains challenging.

Several questions have emerged that need to be answered in the near future: Should cats with asymptomatic HCM/HOCM be treated at all? If yes what drugs are most beneficial and least detrimental? At what stage of the disease should treatment be started? At what time intervals should affected cats be monitored? What are indicators of successful treatment? What are prognostic indicators? Possible exceptions with regard to uncertainties in the treatment of asymptomatic HCM may be cats with severe HOCM and LV hypertrophy, frequent ventricular ectopy, severe LA enlargement, atrial fibrillation, smoke or thrombi in the LA, and radiographic or echocardiographic evidence of congestion. The presence of such striking findings usually represents a strong motivation to initiate pharmacologic treatment, even in the absence of overt clinical signs, with the expectation that it might reduce the hemodynamic burden, delay the onset of clinical signs, and favorably altering the clinical course of the disease.

Beta receptor blockers

Atenolol and propranolol are most frequently used to treat cats with occult HCM. Atenolol is a second-generation, hydrophilic, long-acting, β1-selective adrenergic receptor antagonist. In healthy cats, bioavailability is approximately 90% with a peak beta blocking effect occurring approximately 60 min after oral administration and a mean terminal half-life of 220 min. Twice daily oral dosing for chronic treatment of HCM has been recommended in cats. Propranolol is a first-generation, lipophilic, short-acting, non-selective (β1 and β2 effects) beta blocker. Time to peak plasma concentration after oral administration is similar to that of atenolol.
however elimination half-life is shorter necessitating q8h dosing. Beta receptor blockers are therapeutically used due to their negative inotropic (relief of dynamic obstruction and mid-cavitary obliteration, antiischemic effects), negative chronotropic (antiischemic effect), positive lusitropic (increase of LV filling time, decrease of diastolic calcium leakage from the sarcoplasmatic reticulum calcium stores thus improving relaxation and diastolic filling), and direct antiarrhythmic effects. Long-term treatment (3 to 15 years) in people with HCM using high doses of propranolol has led to a considerable reduction of LV hypertrophy. Although no clinical trials are available to support the use of atenolol in cats with HCM, a recent interim analysis of a prospective, double-blind, multicenter evaluation of chronic therapies for feline diastolic heart failure including 118 cats with CHF suggested that the addition of atenolol to standard furosemide was not of any benefit in terms of survival. However, anecdotal evidence exists that cats with moderate to severe occult HOCM clinically benefit from the administration of atenolol.

### Calcium channel antagonists

Diltiazem, verapamil, and nifedipine have all been used in people with HCM with diltiazem being the most popular drug among veterinary cardiologists for the treatment of feline HCM. Diltiazem is positive lusitropic (improvement of LV relaxation via restoration of Ca²⁺ homeostasis in the sarcoplasmatic reticulum of cardiomyocytes and thus, improvement of LV filling), mild negative inotropic, negative chronotropic, and negative dromotropic (antiischemic effect) drug, causes coronary (and systemic) arterial vasodilation (antiischemic effect), and has antiplatelet activity. Passive LV diastolic properties such as wall stiffness do not seem to be influenced by diltiazem. In most human patients with HOCM treated with diltiazem, systemic vasodilatation does not worsen the LV outflow gradient. However, some people have marked increase in dynamic LV outflow tract obstruction and a potentially harmful elevation of PCWP associated with the administration of diltiazem. Studies in cats assessing the effects of diltiazem on the LV outflow tract pressure gradient are lacking.

In normal cats, oral bioavailability of diltiazem is approximately 70\%. The time to peak concentration and terminal half-life of conventional diltiazem (Cardizem®, Marion Merrill Dow, Kansas City, MO) and sustained release diltiazem (Cardizem® CD) were reported at 45 min and 113 min and 340 min and 411 min, respectively. Therefore, q8h dosing for Cardizem® and q24h dosing for Cardizem® CD have been recommended. Oral diltiazem (Cardizem®) has been studied in cats with HCM and CHF based on a small scale investigation of 12 cats, where a favorable effect of the drug on clinical signs, heart rate, LV hypertrophy, LV diastolic function, peripheral tissue perfusion, and survival was demonstrated. Validation of the results of the latter study in a controlled, prospective, blinded, and large scale study is needed to prove the efficacy of diltiazem in cats with HCM and justifies its recommendation for therapeutic use. Compared to diltiazem, verapamil does not seem to be as effective for treatment of feline HCM.

Another formulation of extended-release diltiazem (Dilacor® XR, Watson Pharmaceuticals, Inc., Corona, CA) has been studied in 10 healthy cats and 28 cats with HCM. Serum concentrations of diltiazem following both the 30 mg and the 60 mg dose q24h were erratic. Dilacor® XR dosed at 30 mg q24h did not lead to stable therapeutic (50-200 ng/ml) blood diltiazem concentration over a 24 h period whereas diltiazem dosed at 60 mg q24h did. However, administration of the higher dose was frequently associated with side effects such as decreased appetite, vomiting, diarrhea, weight loss, and lethargy most likely owning to supratherapeutic diltiazem concentrations seen during the first 12 h post pill. Based on the results of the latter study, the use of sustained-release diltiazem (Dilacor® XR) in cats was not recommended.

### Other drugs

The administration of ACE inhibitors (ACEI) to cats with asymptomatic HCM has been recommended by some investigators, especially when the LA is moderately to severely enlarged. Although ACEI could theoretically potentiate the degree of dynamic LV outflow tract obstruction in cats with HOCM, a small scale study with 12 cats treated with benazepril (0.5 mg/kg q24h) did not reveal worsening of the obstruction due to the ACEI. However, in cats with cardiomyopathy and previously stabilized CHF, the addition of enalapril (0.4-0.6 mg/kg q24h) to standard furosemide was associated with a worse survival as compared to placebo. Moreover, ramipril given to Maine Coon cats with familial HCM but without CHF over a period of 12 months did not change LV mass, severity of myocardial fibrosis as assessed by cardiac MRI, and echo variables of LV diastolic function. Therefore, the early use of ACEI in cats with asymptomatic HCM may not be warranted.

### STUDY OUTLINE

In 2003, a study in cats with occult HCM/HOCM was started. The aim of the initial short-term part of the study was to compare the effects of standard doses of atenolol versus diltiazem on LA function and LV diastolic function in a double-blind crossover clinical study. Thirty one cats were identified and randomized to treatment with either atenolol (Atenolol 25 mg, Zydis Pharmaceuticals, Inc., Princeton, NJ; 6.25 to 12.5 mg q12h) or diltiazem (Dilacor® XR, Watson Pharmaceuticals, Inc., Corona, CA; 30 mg q24h). After 4 weeks, the medication was switched to the alternative drug. Physical examination, Doppler blood pressure measurement, ECG, chest radiography, and echocardiography were done at baseline, at 4 weeks, and at 8 weeks. Serum cardiac troponin I was analyzed in 26 cats and serum diltiazem concentration in 8 randomly selected cats. After completing the first 8 weeks of the study period, the cats were assigned to either atenolol or no treatment in an open label clinical study. The aim of the long-term part of the study is to assess the effects of atenolol on LA size and LA function and LV diastolic function in cats with asymptomatic HCM as compared to untreated cats with HCM. While study 2 is still ongoing, results of study 1 will be presented.

### List of References

KEYWORDS
Beta receptor blockade, calcium channel antagonist, hypertrophic cardiomyopathy, echocardiography, Doppler, left atrium.