THE GREAT APE HEART PROJECT
BASED AT DETROIT ZOO

Therapeutic Considerations for the Treatment of Cardiovascular Disease in Great Apes

This document is intended to serve as a guideline when considering treatment options for common cardiovascular diseases in the great apes. The information contained within this document is based on human and veterinary cardiology guidelines and the combined clinical experience of the Great Ape Heart Project (GAHP) clinical advisory board since its establishment in 2010. The information is not based on pharmacokinetic or pharmacodynamic data of medications in these species. Due to a paucity of available literature regarding the treatment of these diseases and the pharmacokinetic and pharmacodynamic behavior of medications in these species, it is strongly recommended that veterinary clinicians considering treatment options for cardiovascular disease in great apes consider consultation with the GAHP cardiac and SSP or species-specific veterinary advisors, and any local expert consultants prior to initiating cardiovascular therapies. As our knowledgebase pertaining to the diagnosis and management of cardiovascular disease in the great apes expands, the potential therapeutic options will likely change.

The following document is organized based on the underlying cardiovascular disease as determined by echocardiography, electrocardiography, blood pressure assessments, and advanced imaging (in some cases). Dosing guidelines, including background information on drug classes, are also presented. Notably, the cardiac diagnosis is often non-specific in that many disease etiologies, including primary/genetic cardiac disease, can result in a certain phenotype. For example, dilated cardiomyopathy (DCM) can be a primary condition, but it can also result from etiologies that include infectious disease, toxic insults, dietary/nutritional abnormalities, persistent arrhythmia, and infarctions. Further, arrhythmias and hypertension often have systemic (i.e. non-cardiac) etiologies. Accordingly, additional non-cardiac medications may be necessary based on a thorough systemic evaluation. There are some notable differences in the management of cardiovascular disease between animals and humans, and even between domesticated species. Where relevant, these differences will be briefly addressed. Finally, some of the drug classes (ex: beta blockers, ACE-I/ARBs) are dosed based on a titration schedule. The goal with these medications is often not to alleviate clinical signs but to provide long-term therapeutic benefits (i.e. to slow disease progression). For this reason, we recommend following the provided up-titration schedule to achieve the recommended therapeutic dose after titration regardless of a perceived improvement at the starting dosages.

Disease Background

Systemic Hypertension

Based on the American Heart Association's 2017 guidelines, systemic hypertension in humans is defined as blood pressure readings consistently >130/80mmHg with anti-hypertensive medications generally being prescribed when readings are consistently >140/90mmHg.[5]

Hypertension has not been defined in most of the great ape species. It has been defined in a group of healthy, laboratory-housed chimpanzees in one study,[3] however, it remains unknown what blood pressure thresholds correlate to clinical disease and an increased risk of cardiovascular death in any of the great ape species. Further, acquisition of an accurate blood pressure is confounded by the difficulty in obtaining awake measurements in most animals, an inability to ascertain the effect of situational or "white coat" hypertension, diurnal and temporal variability, and a lack of available studies comparing direct (arterial) and indirect measurements. Indeed, both the stress of immobilization and the anesthetic agents used have the potential to profoundly alter readings in anesthetized animals. Lastly, while primary hypertension is common in humans, it is relatively uncommon in domestic species, and it is unknown whether this occurs in the apes.[1] For these reasons, blood pressure assessment in the great apes should be evaluated in the context of concurrent physical exam and clinical findings, and abnormal readings in the absence of other findings would ideally be confirmed on subsequent exams before initiating anti-hypertensive therapy. Antemortem findings suggestive of systemic hypertension include retinal lesions, proteinuria, neurologic signs/findings consistent with stroke, and left ventricular concentric hypertrophy (thickening) with and without concurrent systolic dysfunction.[6,7] Postmortem findings include arteriosclerosis, myocardial fibrosis, hemorrhagic strokes, and aortic dissections.[4]

If anti-hypertensive therapy is warranted, animal and human guidelines recommend either maximizing single-agent therapy before adding in additional medications or using low-dose combination therapy with titrations performed until a target blood pressure is obtained.[1,8] Lifestyle modification, including weight loss, reduced sodium intake, exercise, and stress reduction, is generally recommended in humans prior to beginning anti-hypertensive therapy, and it should also be considered in animals where applicable unless the hypertension is consistently severe (>180mmHg) in which case prompt anti-hypertensive therapy is recommended.

Given the aforementioned limitations in classifying hypertension in apes, a reasonable target blood pressure of <160mmHg is recommended by the GAHP. In animals without systolic dysfunction, consideration should be given to treatment with ACE-inhibitors (ex: lisinopril, enalapril) and/or dihydropyridine calcium channel blockers (ex: amlodipine). For animals with systolic dysfunction, a beta-blocker (ex: carvedilol, metoprolol) in conjunction with an ACE-inhibitor or an angiotensin receptor blocker (ARB) should be considered. Thiazides (ex: chlorthalidone, hydrochlorothiazide) have also been used in apes as part of combination therapy. Diuretics should be used cautiously due to an inability to routinely monitor electrolytes.

References (systemic hypertension):

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Arrhythmia

Arrhythmias have been documented in all four great ape species.[2,4-6] Premature beats originating from both the upper and lower chambers (i.e. APCs and VPCs, respectively) are not uncommon in apes with and without structural disease based on echocardiography. More pathologic arrhythmias, including atrial flutter, atrial fibrillation, and ventricular tachycardia have all been recorded in apes. Bradyarrhythmias (ex: atrioventricular block, sinus arrest) have also been documented in the great apes, but do not appear to be common, clinically relevant conditions at this time.

There are many potential causes of arrhythmia, including structural heart disease (ex: dilated cardiomyopathy, arrhythmogenic cardiomyopathy), electrolyte abnormalities, stress/excitement, pain, infectious/inflammatory diseases (ex: myocarditis), or systemic diseases such as endocrinopathies or neoplasia/cancer (particularly those that involve the spleen, liver, or pancreas). When conducted as single, infrequent abnormal beats, arrhythmia is generally not life-threatening, and patients may not show clinical signs. When VPCs or APCs occur in rapid succession (ex: fast couplets or triplets) or for extended periods of time (ex: ventricular tachycardia, atrial fibrillation, high-grade atrioventricular block), the risk of sudden death, congestive heart failure, and stroke increases. Further, clinical signs such as decreased appetite, collapse/syncope, exercise intolerance, weakness, lethargy, and ataxia/wobbliness may be noted. Arrhythmias are often transient and may be triggered throughout the day by sleep/wake cycles, excitement, or exercise. Treatment is aimed at resolving clinical signs and mitigating the chance of sudden cardiac death from the arrhythmia with antiarrhythmic medications (when indicated) and addressing the underlying cause if one is found. Since stress and anxiety may potentiate certain types of arrhythmia, individual and group management tactics to reduce environmental stressors may also be warranted. Because anti-arrhythmic agents can also be pro-arrhythmic, and because monitoring for a response to treatment and for associated side effects is limited in apes, consultation with the GAHP veterinary and human cardiologists or the local consulting physician is strongly recommended.

Several anti-arrhythmic agents have been used in the great apes, including amiodarone, carvedilol, diltiazem, digoxin, metoprolol, and sotalol. Opportunistic acquisition of 6- and/or 12-lead ECGs is recommended during immobilization procedures, and many institutions are monitoring arrhythmias using the Kardia mobile devices.[1,7] The GAHP is currently utilizing implantable loop recorders in all 4 species to further classify the types of arrhythmia present and the response to therapy. These devices are also being used for continuous monitoring in high-risk animals or in those with increased VPC frequency noted on their exams.

References (Arrhythmia):

1. Barbour CC, Danforth MD, Murphy H, et al. Monitoring great ape heart health through innovative electrocardiogram technology: training methodologies and welfare implications. Zoo Biol. 2020;39:443-447.

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Cardiomyopathy

Cardiomyopathy is a general term used for diseases that affect the heart muscle, and many phenotypes exist (ex: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy, etc.). The echocardiographic phenotype is often non-specific in that various etiologies, including primary/genetic cardiac disease, can result in a certain phenotype. Indeed, the phenotypic appearance may also change temporally as is often seen in cats with HCM who may develop DCM in later stages of their disease. For these reasons, a systemic work-up is generally recommended, and systemic hypertension, infectious or inflammatory etiologies, ischemic coronary disease (believed to be rare in apes), congenital anomalies, and hemodynamically significant valvular regurgitation should be ruled out before a primary/genetic etiology is considered. Treatment is often based on a combination of the echocardiographic phenotype, blood pressure assessments, and electrocardiographic findings.

The long-term management of cardiomyopathy represents an area where treatment recommendations differ somewhat between veterinary and human cardiologists. Optimal therapy has not been established for any cardiomyopathy in apes. Angiotensin converting enzyme inhibitors (ACE-I) are routinely used in both humans and domestic species for various cardiomyopathies.[1,13,19] The most notable management differences pertain to the treatment of DCM, or heart failure with reduced ejection fraction. The usage of beta blockers in this condition has been repeatedly shown to improve survival time in humans,[14,21] while a benefit was not shown in dogs.[15] In humans, they reduce adrenergic tone, reduce myocardial energy demand, mitigate the risk of arrhythmia, and improve both diastolic and systolic function over time.[2,14,17,21] In veterinary patients, pimobendan improves both quality of life scores and survival time in dogs with DCM and heart enlargement from valvular disease in several studies both before and after congestive heart failure (CHF).[3,5,12,20] More recent literature also suggests a potential benefit in cats with various heart diseases.[4,6,18] Initial studies evaluating the use of pimobendan for the management of cardiac disease in humans revealed positive results, including increased quality of life scores, exercise tolerance, and a relatively low side effect profile.[7,9,11,22] These positive results have been confirmed in more recent studies.[8] Notably, however, increased mortality was observed in patients receiving pimobendan as compared to controls in one of two clinical trials.[11] For this reason, clinical development in the human market was widely discontinued in 1996, although it is still used in Japan.[16] In small animal medicine, pimobendan was not shown to increase the frequency of malignant arrhythmias in dogs and cats.[4,10] Both pimobendan and beta blockers have been used for the treatment of DCM and other cardiac diseases in the great apes, with and without underlying arrhythmia.

There are now two new classes of medication sometimes recommended for treatment in humans and dogs with heart failure with reduced ejection fraction: angiotensin receptor neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Due to cost and unknown risk and efficacy in great apes, they have not yet been used.

References (Cardiomyopathy):

1. Amberger CN, Glardon O, Glaus T, et al. Effects of benazepril in the treatment of feline hypertrophic cardiomyopathy: Results of a prospective, open-label, multicenter clinical trial. J Vet Cardiol. 1999;1(1):19-26.

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Valvular Disease

Valvular disease is the most common acquired heart disease in dogs, and it occurs commonly in adult humans.[1,2,4] Often termed degenerative valve disease (DVD), myxomatous degeneration, or valve prolapse, this condition is typically slowly progressive and not all patients develop clinical signs. In elderly humans, sclerosis and calcification of the aortic valve is also well-described.[5] Any valve within the heart can be affected by degenerative changes, but the most affected valve is the mitral valve. With degeneration, the valve leaflets and the chordae tendineae become thickened and irregular. This results in valvular regurgitation. In a subset of human and veterinary patients, the regurgitation becomes substantial enough to cause heart enlargement. At this stage, patients may remain asymptomatic, but medications have been shown to delay the onset of congestive heart failure (CHF) in some species.[2,6] Namely, pimobendan therapy has been shown to delay CHF in dogs with cardiomegaly from DVD by up to 15 months.[2] In humans, ACE-I therapy is often recommended prior to CHF for mitral valve disease especially in those patients with hypertension and/or systolic dysfunction.[6]

Eventually, the pressure within the heart caused by the leak may increase resulting in CHF. Clinical signs associated with CHF vary by species but include lethargy/weakness, exercise intolerance, coughing, abdominal distension, peripheral edema, and/or an increased breathing rate/effort. At this stage, additional medications are recommended (ex: spironolactone, loop-diuretics, ACE-I/ARBs, pimobendan) and often required to prevent or mitigate the clinical signs of CHF.[3] While surgical repair and replacement of the affected valve is considered the gold standard treatment in both veterinary and human patients, this is not widely available in veterinary patients and is often cost-prohibitive. In apes, DVD has been diagnosed in all species, but clinical disease appears to be relatively uncommon at this stage. Infection of the heart valves, termed endocarditis, is exceedingly rare but has been documented in gorillas.[4] This latter condition carries a poor prognosis, and treatment involves broad-spectrum antibiotic therapy for a minimum of 8-12 weeks.

References (Valvular disease):

1. Aupperle H, Disatian S. Pathology, protein expression and signaling in myxomatous mitral valve degeneration: comparison of dogs and humans. J Vet Cardiol. 2012;14(1):59–71.
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Vascular Disease

Aortic Dissection:

Aortic dissections in humans are most prevalent in older individuals and have a sex predilection for males.[3] Systemic hypertension and connective tissue disorders (ex: Marfan syndrome) are common risk factors, and dissections have been reported in gorillas, bonobos, and chimpanzees.[1,2,4] The dissections observed in apes appear most commonly in the ascending aorta (Stanford Type A or DeBakey Types 1 & 2). Surgery and beta blockers represent the mainstay of therapy in humans. Animals with significant aortic dilation on echocardiography and/or those with persistent systemic hypertension should be treated with anti-hypertensive agents due to the potential negative effect of hypertension on aortic dissections and aneurysms.

Coronary Arterial Disease:

While atherosclerosis of the coronary arteries represents the most common cause of cardiac death and congestive heart failure in adult humans, it does not appear to be a significant clinical problem in great apes at this time. Earlier literature from the 60s and 70s suggested that atherosclerosis was a common problem in chimpanzees, but more recent literature and work by the GAHP has found that this is an uncommon clinical problem. For this reason, therapy for atherosclerosis, such as nitroglycerin and statin medications, has not been routinely recommended.

References (Vascular disease):

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Drug Synopses & Dosing Guidelines

Anti-coagulants & Anti-platelet Agents:
Anti-clotting agents are often recommended in humans and cats with significant heart enlargement to mitigate the chance of blood clot formation and secondary thromboembolic disease.[1,6] These medications are also sometimes recommended with certain types of arrhythmia (ex: atrial fibrillation) that predispose patients to stoke.[1] Both anti-coagulant (ex: rivaroxaban, apixaban) and anti-platelet (ex: aspirin, clopidogrel) agents have been studied extensively in small animals & humans and are generally considered relatively safe medications.[3,5] These agents also do not require extensive monitoring when compared to older agents (ex: warfarin). The mechanism of action varies widely, but these agents act to prevent platelet aggregation and activation, and interrupt various components of the clotting cascade.

Due to significant intraspecific aggression and the potential for wounds/injuries and falls in some of the great ape species, the use of these medications may carry a clinically relevant degree of risk for bleeding. Systemic hypertension is also relatively prevalent in some of the species, which may increase the risk of hemorrhagic stroke if antithrombotic agents are used. Lastly, species-specific differences in coagulation factor profiles appear common and likely affect both the efficacy and safety of these agents within a species.[4] To date, there is a dearth of information available regarding the normal coagulation system in the great ape species. With the limited literature available, notable differences have been described within and between species.[2,4,7] For these reasons, caution is advised when deciding on whether to use these medications, and *the GAHP clinical advisory board feels that the anti-coagulant class of medications carries a much greater risk in apes as compared to the anti-platelet medications.*

Reported doses of various anti-platelet agents in apes include:
Aspirin: 81-325mg q24h
Clopidogrel: 75mg q24 (this medication is very bitter when split or compounded)

Reported doses of various anti-coagulant agents in apes include:
Rivaroxaban:15-30mg q24h (this medication is very bitter when split or compounded)

References (Anti-thrombotic agents):

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2. Cate H, Schenk BE, Biemond BJ, et al. A review of studies of the activation of the blood coagulation mechanism in chimpanzees (*Pan troglodytes*). J Med Primatol. 1994;23(5):280-284.
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Angiotensin Converting Enzyme Inhibitors (ACE-I)/Angiotensin Receptor Blockers (ARBs): The renin-angiotensin-aldosterone system (RAAS) is a complex neurohormonal system that is well-conserved across species. This system involves both circulating and tissue components and is responsible for maintaining several aspects of homeostasis.[1,2,4] Given the complexity of this system, which includes both classical and the more recently described alternative pathways, it remains an ever-evolving area of research.

Angiotensin converting enzyme inhibitors (ACE-I) & angiotensin receptor blockers (ARBs) are a well-established component of the management of cardiac disease, systemic hypertension, and a subset of renal diseases across species.[1,2,6] These drugs have anti-hypertensive and anti-fibrotic effects, and they decrease sodium resorption in the kidneys and blunt the activation of RAAS that occurs secondary to diuretic and other anti-hypertensive medications.[1,2] There is also evidence that shows this class of medications (ACE-I) can delay the onset of congestive heart failure with some cardiac disease states[6] and mitigate pathologic remodeling that leads to atrial fibrillation.[3,5]

Side effects are more common with ACE-I when compared to ARBs, however, they are generally mild. Side effects include coughing, angioedema, and pancreatitis.[2] The efficacy of both drug classes is similar in humans for most conditions.[2] Experience with ARBs in the apes is limited, and these are less widely used in the treatment of cardiovascular disease in veterinary patients as compared to ACE-I. They have teratogenic effects and therefore are not used in pregnant animals, and they should be used with caution in animals with certain types of renal disease. A single case-report of probable hepatotoxicity in a gorilla receiving enalapril was published, but it was suspected that the toxicity may have been caused by a combination of the enalapril and indulgent consumption of mulberry browse.[4]

Reported doses of various ACE-I/ARBs in apes include:
Lisinopril: 5mg q24h slowly titrated to 20mg q12h; for larger apes 40mg q12h have been used
Enalapril: 5mg q24h slowly titrated to 20mg q12h; for larger apes 40mg q12h have been used
Benazepril: 5mg q24h slowly titrated to 20mg q24h
Losartan: 50mg-100mg q24h; 25mg q24h could be considered for smaller bonobos
Valsartan: 40mg-320mg q12-24h; no more than 160mg per dose per human guidelines

References (ACE-I/ARBs):

1. Ames MK, Atkins CE, and Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. 2019;33:363-382.
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Beta Blockers:
Beta blockers are routinely utilized in the management of several cardiovascular disorders.[7] They provide anti-arrhythmic and anti-ischemic effects, and they have anti-hypertensive effects via direct and indirect mechanisms.[7] This class of medications can cause bradycardia, sinus & atrioventricular block, lethargy, and hypotension. They are generally considered contraindicated in human & veterinary patients with asthma and should not be prescribed during episodes of decompensated congestive heart failure. Beta blockers are most commonly used in the management of heart failure with reduced ejection fraction (HFrEF) in humans, whereas this class of drugs has not been shown to be beneficial in dogs with similar conditions (ex: dilated cardiomyopathy).[2-5] Notably, the benefit of beta blockers does not generally manifest before 3 months of therapy, and dogs are often diagnosed at more advanced stages of disease when compared to humans. This class of drugs is widely used in both human and veterinary patients in the management of various arrhythmias, and these medications are occasionally added as second or tertiary agents for systemic hypertension.[6]

Beta blockers come in several forms, including beta-1 and beta-2 selective and non-selective agents, and in forms that exert additional properties including alpha and/or potassium channel blockade (ex: carvedilol, sotalol).[1] Unlike in veterinary medicine where sotalol is used predominantly as an anti-arrhythmic agent, this medication is generally not recommended in humans with systolic dysfunction. Studies in human medicine have shown that the cardiac benefits provided by beta blockers are not uniform between agents.[1] Carvedilol is the most commonly used agent in apes and confers both beta and alpha-blocking actions. This agent appears to be superior to others based on several human studies.[1,4] Most agents cross the placenta and are excreted in breastmilk, but teratogenicity and fetotoxicity are not reported in most studies at therapeutic doses. These medications should be tapered over several weeks if discontinuation is recommended/necessary.

Reported doses of various beta-blockers in apes include:
Carvedilol: 3.125mg q12h slowly titrated to 25mg q12h; for larger apes 50mg q12h have been used
Metoprolol tartrate: 12.5mg q12h slowly titrated to 50mg q12h

- *Metoprolol succinate* (long-acting) has not been used in apes to our knowledge

Sotalol: 20mg q12h slowly titrated to 60-80mg q12h; *predominantly used as an anti-arrhythmic agent*

References (Beta blockers):

1. Abbot JA. Beta-blockade in the management of systolic dysfunction. Vet Clin Small Anim. 2004;34:1157-1170.
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Pimobendan:
Pimobendan is a benzimidazole-pyridazinone derivative that acts as a vasodilator and positive inotrope (inodilator) via its calcium sensitization of the cardiac myocytes and inhibitory effect on phosphodiesterase III in both cardiac myocytes and vascular endothelial cells.[1]

In veterinary patients, pimobendan improves both quality of life scores and survival time in dogs with various cardiac conditions, namely valvular disease and dilated cardiomyopathy. These benefits are conferred before and after decompensated/congestive heart failure.[1,3,9,11] More recent literature also suggests a potential benefit in cats with various heart diseases.[2,4,10] Initial studies evaluating the use of pimobendan for the management of cardiac disease in humans revealed positive results, including increased quality of life scores, exercise tolerance, and a relatively low side effect profile.[6,8,12] These positive results have been confirmed in more recent studies.[5] Notably, however, increased mortality was observed in patients receiving pimobendan as compared to controls in one of two clinical trials.[8] For this reason, clinical development in the human market was widely discontinued. In small animal medicine, pimobendan was not shown to increase the frequency of malignant arrhythmias in dogs and cats.[2,7]

Reported doses of pimobendan in apes include:
Pimobendan: 5-40mg q12h; starting dose in cats/dogs is 0.2-0.3mg/kg q12h; this dose also used in apes

References (Pimobendan):

1. Boswood A, Haggstrom J, Gordon SG, et al. Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study – a randomized clinical trial. J Vet Intern Med. 2016;30:1765-1779.
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Calcium Channel Blockers:

Amlodipine is a long-acting dihydropyridine calcium channel blocker, which inhibits calcium influx into vascular smooth muscle cells resulting in decreased vascular tone and a reduction in systemic blood pressure.[1,3] This medication is often employed as a first-line anti-hypertensive agent in both humans and animals. Because of their antiproteinuric effect, ACE-I/ARBs are generally preferred as first-line treatment in patients with chronic renal disease and hypertension.[1,3,4,6] Further, because calcium channel blockers preferentially dilated the afferent renal arteriole, the use of amlodipine as a monotherapy for hypertension in patients with significant proteinuria should be avoided due to concerns for worsening glomerular hypertension.[1] In animals, amlodipine tends to be a more effective anti-hypertensive agent when compared to ACE-I or ARBs alone.[1] For this reason, amlodipine is preferred in the setting of severe hypertension in veterinary patients.[1] In patients with proteinuria and severe hypertension, coadministration of amlodipine and ACE-I/ARB therapy may be an appropriate first-line treatment. Dual therapy with amlodipine and an ACE-I/ARB is common practice in veterinary and human medicine and has been shown in several studies to be superior to monotherapy with amlodipine.[2,3,5] Side effects of amlodipine are uncommon but include peripheral edema, lethargy, headaches, gingival hyperplasia, and nausea.[3] Due to compliance issues, unknown efficacy and safety profiles, and a relative inability to closely monitor blood pressure and systemic effects in apes, it may be prudent to maximize monotherapy before considering dual therapy. Amlodipine is not teratogenic.

Reported doses of calcium channel blockers in apes include:
Amlodipine: 1.25–10mg (0.1-0.2mg/kg) q24h

References (Calcium channel blockers):

1. Acierno MJ, Borwn S, Coleman AE, et al. ACVIM consensus statement: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. J Vet Intern Med. 2018;32:1803-1822.
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Diuretics:
Diuretics are predominantly used for the relief of clinical signs associated with congestive heart failure (CHF), including labored breathing, peripheral edema, exercise intolerance, coughing, and ascites.[8] They are occasionally added in earlier phases of cardiac disease as preload and afterload reducers, however, this is generally not recommended given the potential adverse effects. Occasionally, this class of medications is used as an add-on agent for the treatment of systemic hypertension.[7,8] These drugs are potent activators of the renin-angiotensin-aldosterone system (RAAS), which can adversely affect the heart, blood vessels, and kidneys with long-term usage.[2,4] For this reason, this class of drugs should not be used as sole therapy, and diuretics are generally used concurrent with medications that block RAAS. Further, the inability to consistently monitor electrolyte levels, blood pressure, and kidney values in the great apes necessitates further consideration to using diuretics prior to the onset of clinical signs.

The use of spironolactone, an aldosterone receptor antagonist often labeled as a potassium-sparing diuretic, has been associated with reduced morbidity and mortality in both humans and dogs with a history of CHF.[1,5] Spironolactone also reduced the risk for the development of atrial fibrillation in dogs with dilated cardiomyopathy.[3] For this reason, it is generally considered part of standard therapy for advanced CHF. In small animals, spironolactone is regularly administered in conjunction with ACE-I/ARB therapy without a clinically relevant alteration of potassium levels.[6] Indeed, the combination is generally beneficial to counteract the often-significant potassium loss associated with diuretic medications in dogs and cats. In humans, hyperkalemia is considered a risk factor, however, in a large-scale study evaluating the efficacy of spironolactone in humans receiving concurrent diuretic & ACE-I therapy, the incidence of serious hyperkalemia was minimal.[5] Gynecomastia and breast pain have been reported in men receiving spironolactone.[5]

Reported doses of diuretics in apes include:
Chlorthalidone: 12.5-25mg q24h
Furosemide: 20-160mg q12-24h
Hydrochlorothiazide (Aldactazide): 12.5-25mg q12-24h; higher doses used in large animals
Torsemide: 5-20mg q12-24h; the dose in humans rarely exceeds 200mg/day

Reported doses for spironolactone in apes include:
Spironolactone: 25-50mg q24h; notably, the dose is much higher in small animal (1-2mg/kg q12-24h)

References (Diuretics):

1. Coffman M, Guillot E, Blondel T, et al. Clinical efficacy of a benazepril and spironolactone combination in dogs with congestive heart failure due to myxomatous mitral valve disease: The Benazepril Spironolactone STudy (BESST). J Vet Intern Med. 2021;35:1673-1687.
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