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Review

Geriatric Cardiology in Dogs - Part 2: Challenge with HF Therapy in Geriatric Dogs: Adverse Drug Reactions and Comorbidities

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Abstract

In geriatric dogs, aging-specific changes in cardiovascular physiology, drug metabolism, drug pharmacokinetics and drug tolerance contribute to adverse drug reactions (ADRs). Comorbidities can also cause polypharmacy and thus drug-drug interactions. Adverse drug reactions for ACE inhibitors, β–blockers, furosemide, aldosterone antagonists and digoxin are common. Geriatric cardiology epitomizes the principle that cardiovascular disease is only 1 component of a larger, multidimensional disease state with concomitant geriatric syndromes. Comorbidities (cardiorenal syndrome, hypertension, diabetes mellitus, atherosclerotic disease, metabolic syndrome, obesity, chronic obstructive pulmonary disease and frailty and cognitive dysfunction) are common, aggravate HF, complicate therapy and increase the total heart failure burden.

Keywords: *Geriatric cardiology, Adverse drug reactions, Comorbidities, Dog*

Köpeklerde Geriatrik Kardiyoloji - Bölüm 2: Geriatrik Köpeklerde Kalp Yetmezliği Tedavisinde Zorluklar: İlaç Reaksiyonları ve Komorbitler

Öz

Geriatrik köpeklerde yaşa bağlı kardiyovasküler fizyoloji, ilaç metabolizması, ilaç farmakokinetiği ve ilaç töleransındaki değişiklikler ilaç yan etki reaksiyonlarına yol açar. Komorbitler de polifarmasiye ve böylece ilaç-ilaç etkileşimlerine neden olabilir. ACE inhibitörleri, β-blokörler, furosemid, aldosteron antagonistleri ve digoxin'e karşı ilaç reaksiyonları yaygındır. Geriatrik kardiyoloji, kardiyovasküler hastalığın geriatrik sendromlarla birlikte çok boyutlu bir oluşumun bir komponentini temsil eder. Komorbidler (kardiyorenal sendrom, hipertansiyon, diabetes mellitus, atherosklerotik hastalık, metabolik sendrom, obesite, kronik obstrüktif pulmoner hastalık ve güçsüzlük ve kognitif disfonksiyon) yaygındır, kalp yetmezliğini şiddetlendirirler ve tedaviyi komplike hale getirirler.

Anahtar sözcükler: *Geriatrik kardiyoloji, İlaç yan etkileri, Komorbitler, Köpek*

INTRODUCTION

Whereas cardiovascular (CV) guidelines and standards of care are oriented toward younger adults, most clinicians devise individual strategies to optimize care for their geriatric patients. Indeed, many cardiologists are adept at integrating patient-centered priorities with existing medical science. Nonetheless, the principles of geriatric medicine combined with management and process for older CV patients are not standardized, and core quality metrics for measuring patient-centered outcomes are not sufficiently delineated to teach, implement, or monitor [1]. Since elderly patients differ from non-elderly patients and develop changes in cardiovascular physiology and metabolism, pharmacotherapy must consider aging-specific changes in cardiovascular physiology, drug metabolism, drug pharmacokinetics and drug tolerance, as well as comorbidities, polypharmacy and drug-drug interactions that contribute to adverse effects [1,2].

ADVERSE DRUG REACTIONS

Treatment of the geriatric dogs with heart failure (HF) is not optimal. Polypharmacy is common and can lead to drug interactions, raising issues of efficacy and safety [3].

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Adverse Drug Reactions for ACE Inhibitors

In general, ACE inhibitors should be discontinued if life-threatening adverse drug reactions (ADRs) develop, including angio-edema and anuric renal failure. Caution is advisable in geriatric dogs with low blood pressure (<90 mmHg), high serum creatinine (>3 mg/dL) or high serum potassium (>5 mEq/L) levels. Renal function and serum potassium should be monitored at frequent intervals [2,4].

ACE inhibitors are thought to minimize the hypertrophic process in blood vessels and the myocardium and to retard the process of abnormal collagen deposition. It is important to note that much of the beneficial effect of ACE inhibitors stems from their ability to block bradykininase, thus increasing the beneficial effects of bradykinin. Because nonsteroidal anti-inflammatory drugs (NSAIDs) block the bradykininase inhibition of ACE inhibitors, the use of NSAIDs with ACE inhibitors is contentious [3].

Since fluid retention blunts the therapeutic effects of ACE inhibitors and fluid depletion potentiates ADRs, fluid balance should be monitored and a diuretic given prior to and during ACE inhibitor therapy [1].

Persistent cough, anuric renal failure and angioedema warrant discontinuation of the ACE inhibitor and replacement by an ARB. However, this requires caution since ARBs can also lead to angioedema [5,6].

Adverse Drug Reactions for β-Blockers

ADRs include reactive airways disease (asthma), fluid retention, fatigue, bradycardia (sick sinus syndrome, and second- or third-degree heart block) and hypotension [2]. Rather than discontinue the β-blocker, fluid retention should be treated with a diuretic with concurrent monitoring for excessive weight gain (>2 kg/day) [1].

Fatigue usually resolves within several weeks but may require dose adjustment. In the very elderly, fatigue may be due to comorbidities (e.g., anemia) or concurrent medications [1].

Treatment of HF symptoms is complicated by orthostasis. Evidence of organ hypoperfusion or worsening of renal function may require withdrawal of the β-blocker [1].

Bradycardia and hypotension are more common with carvedilol owing to (α_1-blockade, resulting in light-headedness, dizziness or blurred vision that alarm the very elderly and may lead to falls. Volume depletion may exacerbate hypotension. Care should be taken not to use beta-blockers until the geriatric dog is stable, because these agents can exacerbate the signs of overt heart failure [2].

Adverse Drug Reactions for Furosemide

Reduced circulating blood volume and/or blood pressure will stimulate the RAAS, which is the argument for adding an ACE inhibitor or an aldosterone antagonist to dogs treated with furosemide [2].

Adverse Drug Reactions for Aldosterone Antagonists

Close monitoring of renal function and serum potassium should be performed when using aldosterone antagonists, especially in the geriatric dogs [2]. Since the use of aldosterone antagonists in patients with renal dysfunction increases the risk of hyperkalemia and this risk is greater in the elderly and those receiving an ACE inhibitor or ARB concurrently, spironolactone or eplerenone should be used at a low dose under those circumstances and avoided in those with a creatinine clearance under 30 mL/min. Gynecomastia can occur in 10% and hyperkalemia in 2% of treated human patients [1].

Adverse Drug Reactions for Digoxin

Common ADRs are nausea and vomiting (10%), visual disturbances (15%), cardiac arrhythmias and heart block (3%), in humans [1]. The geriatric dogs should be closely monitored for these ADRs as well as drug-drug interactions, and the dose of digoxin reduced if amiodarone or verapamil are used [2].

COMORBIDITIES

Geriatric cardiology epitomizes the principle that CVD is only 1 component of a larger, multidimensional disease state with concomitant geriatric syndromes. Selection of assessments and therapies is best accomplished in the context of the aggregate circumstances [1].

Comorbidities are common, aggravate HF, complicate therapy and increase the total HF burden. Cardiorenal syndrome, hypertension, diabetes mellitus, atherosclerotic disease, metabolic syndrome, obesity, chronic obstructive pulmonary disease and frailty and cognitive dysfunction need to be targeted early and aggressively with appropriate measures to prevent progression to HF stage D [3,7].

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) occurs when worsening renal function limits diuresis despite clinical volume overload associated with HF. In dogs being treated for chronic HF, declining renal function should be anticipated. The diagnostic marker for chronic kidney disease (CKD), isosthenuria, cannot be relied upon in dogs being treated with diuretics. Monitoring of creatinine especially should be used to discern trends in renal function. A progressive rise even within the normal range should alert the practitioner, along with clinical signs: PU/PD, hyporexia, anorexia, weight loss and vomiting. Goals of treatment are to recognize CRS, reverse it as much as possible and deal with the renal consequences of HF and the complex relationship between HF and renal injury. The difficult balance is to “dry out” the HF and hydrate the kidneys.

Different therapeutic strategies are based upon the degree of compromise of each organ [2].

ACE inhibitors are the mainstay of therapy for CRS especially in the presence of hypertension or proteinuria. Dogs with CRS should be hydrated before starting therapy. Low dose benazepril or enalapril 0.25 mg/kg q 24 h can be increased to proved better control for HF. Benazepril is metabolized in the liver, Enalapril in the kidneys. Therefore, dogs with CRS may need a lower dose of enalapril than benazepril. Initiation of therapy may show a transient increase in BUN/creatinine concentrations. If persistent, lowering the dose is usually sufficient [3].

If azotemia is becoming a concern, the first step is to lower the dose of diuretics. The goal is to find the lowest effective dose that controls HF. The dose must be continuously reassessed. The ideal dose for an individual patient achieves the threshold rate of drug excretion. Adequate natriuresis can be grossly assessed by observation of increased urine volume and decreased specific gravity. Periodic drainage of pleural fluid or ascites can be used to avoid excessive diuretic use [3].

In the event that diuretic resistance occurs, several options are available to correct fluid balance. A CRI of furosemide (0.3-0.6 mg/kg/h IV inhibits sodium resorbtion more effectively than oral or IV boluses. Once the volume overload has resolved, most cats will again respond to oral therapy. Another loop diuretic, torsemide has superior diuretic action and long half-life (0.2 mg/kg PO q 12 h). It appears to be 10 times more potent than furosemide. Dual-diuretic therapy can be considered when furosemide dose needs to be decrease. Spironolactone (1-2 mg/kg q 12 h) may cause severe facial pruritus and must be used with caution [3].

Systemic hypertension is common in CKD and by increasing afterload increases the cardiac workload. Hypertension worsens both CKD and HF. If present, amlodipine (0.0625-0.25 mg/cat PO q 24 h) should be added. Blood pressure monitoring is critical to avoid the effects of iatrogenic hypotension [2,8].

In advanced CRS, a positive inotrope (pimobendan) may improve azotemia, demeanor and appetite and allow reduction in diuretic dose [2].

Dietary modification should consider both conditions. Sodium restriction and Lower phosphorus diets may be helpful in managing kidney disease but may result in the loss of lean body condition. High quality protein should be given to the level that it does not worsen azotemia. Omega-3 polyunsaturated fatty acids have been shown to be beneficial in both cardiac and renal conditions [2,3].

Fluid administration is a balance between improving renal blood flow without precipitating congestive HF. Fluids should be given slowly to correct azotemia, tailored to the individual's ability to tolerate. Abrupt changes in weight, a new gallop heart sound and/or heart rate may indicate impending congestive event and justify fluid rate reduction. Sometimes a low-dose CRI of furosemide will be indicated concurrently in dogs with end-stage CRS. SQ fluids may be less likely to trigger a congestive event and can be given every 24-48 h via a balanced electrolyte solution and adjusted to the individual patient's ability to tolerate. In fragile patients, a smaller volume of fluids may be necessary, titrating slowly upward if the expected effect on uremia is not evident. Electrolytes should be monitored closely, especially potassium, as hypokalemia can trigger arrhythmia. Correction can take place through fluid therapy or oral means [2,8]. Although renal function may remain stable for a period of time in dogs with HF, when CRS occurs it leads to frequent hospitalization, difficulty maintaining good quality of life and eventually euthanasia [2,3].

Hypertension and Heart Failure

Hypertension increases the cardiac workload by increasing afterload. There is a critical role of hypertension in the pathogenesis of HF. Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF [2,9,10]. Also, hypertension is frequently accompanied by metabolic risk factors and obesite, which themselves increase the risk of HF. On the basis of the 44-year follow-up data of the Framingham Heart Study, 75% of patients with HF have antecedent hypertension [11]. In humans, both acute and chronic hypertension have been linked to the risk of HF. Sudden elevation of blood pressure (such as in hypertensive emergencies) can lead to acute left ventricular strain and acute HF [12] and is a common precipitating cause for decompensation in a patient with chronic HF [8]. Progression from chronic hypertension to structural ventricular changes and then to asymptomatic diastolic and systolic ventricular dysfunction is well established by longitudinal epidemiological studies, such as the Framingham Heart Study [9].

Elevated blood pressure places greater hemodynamic burden on the myocardium and leads to left ventricular hypertrophy. Left ventricular hypertrophy is associated with increased myocardial stiffness and decreased compliance, initially during exercise and subsequently at rest [2,13,14]. The initial concentric hypertrophy (thick wall, normal chamber volume, and high mass-to-volume ratio) helps keep wall tension normal despite high intraventricular pressure. Because systolic stress (afterload) is a major determinant of ejection performance, normalization of systolic stress helps maintain a normal stroke volume despite the need to generate high levels of systolic pressure [2,15].

Aggressive control of blood pressure is the most effective approach to reduce the incidence of HF in a hypertensive population. Primary prevention trials have demonstrated up to a 50% reduction in the incidence of HF in patients with hypertension who are treated with blood pressure-

lowering agents [16]. The Hypertension in the Very Elderly trial achieved a 64% relative risk reduction in heart failure with the diuretic indapamide, with or without the angiotensin-converting enzyme (ACE) inhibitor perindopril [17].

Inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) appears to exert a greater benefit on left ventricular hypertrophy and remodeling than would be predicted from their pressure-lowering effect. Their effectiveness in reducing morbid events in nonhypertensive patients with atherosclerotic disease may involve pressure-independent as well as pressure-dependent mechanisms [18].

β-Blockers are also effective in preventing HF in hypertensive geriatric dogs, partly through pressure reduction and partly through inhibition of structural remodeling of the left ventricle. Diuretic therapy also is effective in preventing heart failure, not only through blood pressure reduction but also by intravascular volume contraction, which reduces the risk of congestion. Diuretics are not known to affect remodeling directly. Calcium channel antagonists, especially amlodipine, contribute to prevention of heart failure by their powerful vascular effects that reduce blood pressure and diminish reflected waves [2].

Diabetes Mellitus and Heart Failure

Diabetes and insulin resistance are important risk factors for the development of HF [19]. The presence of clinical diabetes mellitus markedly increases the likelihood of HF in patients without structural heart disease and adversely affects the outcomes of patients with established HF [20,21]. The Framingham Heart Study showed that the prevalence of heart failure was twice as high among diabetic men and five times as high among diabetic women aged between 45 and 74 years as in age-matched nondiabetic controls [22]. After the age of 65 years, the association became even stronger, with a fourfold higher prevalence in diabetic men and an eightfold higher prevalence in diabetic women [22]. HF is the most common admission diagnosis for diabetic patients, and more than one third of patients with type 2 diabetes die of heart failure [23,24]. There is no date on this concern in dogs.

The basic reason for the increased prevalence of HF among diabetic patients is the presence of a distinct diabetic cardiomyopathy that is structurally characterized by cardiomyocyte hypertrophy, microangiopathy, endothelial dysfunction, and myocardial fibrosis [25]. At the cellular level, diabetic cardiomyopathy is associated with defects in subcellular organelles and downregulation of catecholamine receptors as a result of chronically elevated catecholamine levels [26]. Also, in animal models with the onset of hyperglycemia, changes in myocardial calcium transportation and alterations in contractile proteins occur, both of which lead to systolic and diastolic dysfunction that worsens as the collagen content of the myocardium increases [27]. Doppler imaging studies have been used to provide load-independent assessments of cardiac relaxation. These studies not only have confirmed evidence of diastolic dysfunction in asymptomatic patients with diabetes but also have demonstrated a direct relationship between the extent of diastolic dysfunction and glycemic control [28]. Although diastolic dysfunction is the hallmark of diabetic cardiomyopathy, concomitant subtle systolic dysfunction is present even at earlier stages of the disease [23].

Fasting glucose levels are predictive of hospitalizations for congestive heart failure, with a 10% increase in the risk of heart failure-related hospitalization for each 18 mg/dL increase in fasting glucose level [29]. The choice of oral hypoglycemic agent that may be used is restricted. For instance, metformin is contraindicated in the presence of either HF or renal impairment, and precautions also apply to the use of the thiazolidinediones [30,31]. In addition to treating hyperglycemia, it is crucial to control all other cardiovascular and metabolic risks and to prevent complications in patients with diabetes. ACE inhibitors or ARBs can prevent the development of end-organ disease and the occurrence of clinical events in diabetic patients, even in those who do not have hypertension [32]. Long-term treatment with several ACE inhibitors or ARBs has been shown to decrease the risk of renal disease in diabetic patients [33,34], and prolonged therapy with the ACE inhibitor ramipril has been shown to lower the likelihood of heart failure, myocardial infarction, and cardiovascular death [32]. Likewise, the use of ARBs in patients with diabetes mellitus and hypertension or left ventricular hypertrophy has been shown to reduce the incidence of first hospitalization for heart failure, in addition to having other beneficial effects on renal function [35,36].

Atherosclerotic Disease and Heart Failure

Patients with known atherosclerotic disease (e.g., of the coronary, cerebral, or peripheral blood vessels) are at increased risk of developing heart failure. Although it is less common in dogs, coronary atherosclerotic disease can lead to acute or chronic ischemia, thereby predisposing to left ventricular dysfunction and symptomatic heart failure [2].

ACE inhibitors reduce incidence of heart failure by 23% among patients who have coronary artery disease and normal systolic function and by 37% among patients who have reduced left ventricular systolic function, in humans. Observational studies and small clinical investigations have suggested that hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) may be beneficial in patients with ischemic and nonischemic heart failure [1].

Metabolic Syndrome and Heart Failure

The term "metabolic syndrome" refers to a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus. According to the National Cholesterol Education Program Adult Treatment Panel III, metabolic syndrome

is diagnosed when three or more of the following five risk factors are present [36]: (1) fasting plasma glucose of 100 mg/dL or higher; (2) high-density lipoprotein (HDL) cholesterol level lower than 40 mg/dL in men or lower than 50 mg/dL in women; (3) triglyceride levels of 150 mg/dL or higher; (4) waist circumference of 102 cm or more in men or 88 cm or more in women; and (5) systolic blood pressure of 130 mmHg or higher or diastolic blood pressure of 85 mm Hg or higher, or the presence of drug treatment for hypertension.

The prevalence of metabolic syndrome reaches epidemic levels and ranges from 6.7% among people 20 to 29 years of age to 43.5% for people 60 to 69 years of age and 42.0% for those 70 years of age or older [37,38].

Mechanisms underlying elevated cardiovascular risk associated with metabolic syndrome appear to involve subclinical organ damage [39]. Among patients with hypertension but without diabetes, those with metabolic syndrome seem more likely to have microalbuminuria, left ventricular hypertrophy, and increased carotid intima thickness than did those without metabolic syndrome [39]. In addition, the greater the number of metabolic syndrome components present, the more severe were the microalbuminuria and left ventricular hypertrophy [39].

Treatment of metabolic syndrome consists of aggressive management of each of its individual components, including impaired fasting glucose concentration, dyslipidemia, and hypertension. Drugs targeting nuclear peroxisome proliferator-activated receptors (PPARs) PPAR-α (e.g., fenofibrate and gemfibrozil) are used in the treatment of metabolic syndrome. Fibrates decrease triglyceride level, increase HDL cholesterol, and may have some anti-inflammatory effects; however, their effect on cardiovascular disease outcomes continues to be evaluated [40]. Among patients with impaired glucose tolerance and cardiovascular disease or risk factors, the use of the ARB valsartan along with lifestyle modification led to a relative reduction of 14% in the incidence of diabetes but did not reduce the rate of cardiovascular events [41].

Obesity and Heart Failure

In several studies, obesity has been associated consistently with left ventricular hypertrophy and dilation ,which are known precursors of heart failure [42-44]. In the Framingham Heart Study population, overweight, lesser degrees of obesity and extreme obesity were associated with an increased risk of HF [45,46].

There are several plausible mechanisms for the association between obesity and heart failure. Obesity is a risk factor for hypertension [47] diabetes mellitus [47,48], and dyslipidemia, all of which augment the risk of myocardial infarction [22,49], an important antecedent of HF, in humans. Adipose tissue acts as an endocrine organ, secreting hormones and other substances that create a proinflammatory state and promote formation of atherosclerotic plaques [50].

In humans, a number of strategies have been used to treat obesity, including diet, exercise, behavior therapy, medications, and surgery. To select among these treatments, clinicians must evaluate the obesity-related risks to the individual patient and balance those risks against any possible problems with the treatment. Because all medications inherently carry more risks than do diet and exercise, medications should be chosen only for people in whom the benefit justifies the risk [51,52].

Chronic Obstructive Pulmonary Disease and Heart Failure

The importance of COPD as a cause of death is probably underestimated, in as much as COPD is probably a contributor to other common causes of death, in humans [53]. The risk ratio of developing heart failure in patients with COPD is 4.5, in comparison with age-matched controls without COPD, after adjustments for cardiovascular risk factors [54]. Among the comorbid conditions commonly associated with HF, COPD is the one that most delays the diagnosis of heart failure and is most often blamed for nonadherence to therapeutic guidelines, especially β-blockade [55].

A working hypothesis to account for the high prevalence of left ventricular systolic dysfunction in patients with COPD is that low-grade systemic inflammation in COPD accelerates progression of coronary atherosclerosis, which ultimately results in ischemic cardiomyopathy. Such a hypothesis is based on the fact that patients with COPD have higher elevation of inflammatory markers [56,57], and it fits the clinical observation of a higher incidence of troponin elevation [56] and left ventricular wall motion abnormalities [58] noted in patients with COPD and left ventricular dysfunction. Patients with HF and concomitant COPD have higher activation of neurohormones, particularly norepinephrine and plasma rennin [56]. COPD may also lead to right ventricular failure from pulmonary hypertension, a common complication of COPD [59]. The cause of pulmonary hypertension in COPD is generally assumed to be hypoxic pulmonary vasoconstriction [2,59].

Bronchodilators, corticosteroids, and antibiotics in the treatment of acute exacerbations constitute the mainstay of current drug therapy for COPD [60]. Long-term oxygen therapy was also shown to reduce mortality and improve quality of life in patients with severe COPD and chronic hypoxemia (partial pressure of arterial oxygen <55 mm Hg) [61]. The presence of COPD affects the treatment of HF, in as much as COPD is still viewed as a contraindication to β-blockade. Therefore, patients with HF caused by left ventricular systolic dysfunction who also have COPD are often deprived of the most beneficial pharmacological intervention. A large body of data indicates that patients with COPD may tolerate selective β-blockade, and these

medications should not necessarily be denied to patients with heart failure and concomitant COPD [19,62].

Frailty and Cognitive Dysfunction and Heart Failure

Other problems such as frailty and cognitive dysfunction common in the elderly HF patient can also complicate management [4]. Frailty and cognitive impairment are common and lead to reduced compliance. Response to diuretics, ACE inhibitors, β-blockers and/or positive inotropes may be diminished [4].

Cognitive dysfunction (CD) lead to polypharmacy. The most common signs of CD are disorientation in time and space, altered learning, house soiling, altered interactions (e.g. attention seeking, anxiety, irritability), changes in activity (wandering or pacing), changes in sleep patterns, decreased appetite and increased vocalization [63].

Therapies extrapolated from studies in humans and dogs include anti-oxidant enriched diets, supplements phosphatidyserine, omega-3 fatty acids, Vitamins E and C, L-carnitine. SAMe improved activity and awareness in dogs. Selegiline (Anipryl), which has been anecdotally reported to be proven beneficial in dogs for CD. Environmental enrichment have often been recommended. Any changes should take place slowly [2,63].

CONCLUSION

In geriatric dogs, aging-specific changes in cardiovascular physiology, drug metabolism, drug pharmacokinetics and drug tolerance contribute to ADRs. Comorbidities can also cause polypharmacy and thus drug-drug interactions.

Comorbidities (cardiorenal syndrome, hypertension, diabetes mellitus, atherosclerotic disease, metabolic syndrome, obesity, chronic obstructive pulmonary disease and frailty and cognitive dysfunction) are common, aggravate HF, complicate therapy and increase the total HF burden.

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