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Role of Amlodipine and Hydralazine in the Management of Chronic Mitral Valve Degeneration

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Review Article

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ABSTRACT

This comprehensive review explores the potential of amlodipine and hydralazine as major treatments for chronic mitral valve degeneration in dogs. Focusing on their mechanisms as arterial dilators, the paper evaluates the effectiveness of these agents in the context of both human and veterinary medicine. While hydralazine has seen varying degrees of success and acceptance in human patients due to its mixed results in long-term treatments, amlodipine has shown promising outcomes without significant side effects. The review highlights the need for further species-specific studies to better understand the applicability and effectiveness of these drugs for canine chronic mitral valve degeneration, proposing a potential shift in the pharmacological management strategies for canine mitral regurgitation.

Keywords: Hydralazine; Amlodipine; Afterload reduction; Chronic mitral regurgitation

INTRODUCTION

Chronic Mitral Regurgitation (MR) due to Myxomatous Mitral Valve Disease (MMVD) is the most prevalent cardiac disease in dogs. It ultimately causes congestive heart failure (i.e., pulmonary edema) in roughly 30% of cases [1,2]. While numerous pharmacological management strategies aimed at postponing the onset or recurrence of heart failure have been tried, only loop diuretics and pimobendan are unequivocally beneficial [3]. Despite recent advancements in surgical and interventional techniques, their practical application remains constrained by high costs, extensive equipment needs, and the requirement for specialized personnel [4]. Consequently, pharmacological strategies remain the primary mode of management for MR.

Research into the pharmacological management of MR in dogs began in earnest in the 1980s and has persisted into the present [5]. Consensus statements from the American College of Veterinary Internal Medicine (ACVIM) have summarized the findings from these studies. These statements endorse the use of loop diuretics and pimobendan as well as medications that predominantly target the Renin-Angiotensin-Aldosterone System (RAAS), including ACE inhibitors like enalapril and benazepril, and aldosterone antagonists such as spironolactone [3]. These are identified as key therapeutic interventions for MR. However, the limitations of these primary medications in effectively managing refractory MR are apparent, prompting the inclusion of supplementary minor treatments into these statements.

This underscores the need for additional pharmacological agents that could significantly improve MR management. Previous research in both human and veterinary medicine has provided notable success in the concept of afterload reduction therapy *via* systemic arterial vasodilators [6-16]. These agents dilate systemic arterioles and so reduce the resistance to blood flow through the systemic arterial vasculature. This result in an increase in forward blood flow out of the left ventricle (into the aorta) and a reduction in blood flow backward through the mitral valve. The reduction in regurgitant volume results in a decrease in left atrial pressure and so lessening of pulmonary edema formation. Arterial dilating agents can be effective in the pharmacological treatment of heart failure regardless of etiology [6,8,10-12,17,18], but, are notably most successful in the management of heart failure induced by MR.

Although research on some of these drugs in humans has been disappointing [12,16,19-22], it has not been sufficient to undermine the basic theory of afterload reduction therapy itself. In this context, this review considers hydralazine and amlodipine, key afterload reducers, as meriting renewed focus and intensified research in the pharmacological treatment of MR in dogs. In the past these agents have garnered considerable attention in the treatment of human heart failure, backed by substantial research [6-12,14-16,23].

However, since MR is primarily treated interventionally or surgically in human medicine interest in using these drugs to treat MR has waned. In addition, translating these findings to veterinary medicine is complicated by differences in disease presentation and interspecies variation. Thus, there exists a critical demand for more targeted veterinary-specific research and reevaluation of the impacts of these drugs on MR, to determine their potential as adjunctive treatment for chronic MR due to MMVD in dogs [24-30].

The brief history of hydralazine in the context of afterload reduction therapy for congestive heart failure in human

Hydralazine is an arterial vasodilator that acts exclusively on arteries without affecting veins [7,9]. During the mid-1970s to the 1980s, there was significant research interest in arterial vasodilators for afterload reduction therapy in patients with human congestive heart failure. During this period, hydralazine was at the forefront of research into afterload reduction for heart failure patients [29]. Studies on this drug were categorized into short-term and long-term treatment effects, which, however, showed notably conflicting results [6-8,10-12,19,31-36].

In short-term afterload reduction studies for patients with congestive heart failure, hydralazine demonstrated remarkable positive outcomes [6], yielding results that aligned well with the expected benefits of afterload reduction

theory for such patients.

However, long-term treatment with hydralazine in humans showed considerably negative results [6,12,14,19]. According to Packer, long-term studies of hydralazine failed to demonstrate clear advantages over placebo groups [12,22,21]. Although there were beneficial effects in short-term treatments, these were offset in long-term therapy by compensatory vascular constriction and RAAS activation, which led to volume expansion [15,25,26]. Additionally, side effects such as headaches, tachycardia, gastrointestinal disorders, and edema deemed it unsuitable for prolonged use [37-39].

Thus, long-term trials of hydralazine in patients with congestive heart failure were profoundly disappointing, and these studies largely diminished the hopes and expectations for hydralazine as a new therapeutic agent for heart failure [12]. As a result, the early enthusiasm for using hydralazine in the management of heart failure in human medicine gradually waned from the 1980s into the 1990s.

Arterial dilator therapy in congestive heart failure: A lingering promise amid challenges

Despite the challenges associated with the long-term use of hydralazine in patients with congestive heart failure, including a lack of significant improvement over placebo and systemic side effects leading to drug discontinuation, there are still compelling reasons to continue its consideration in heart failure management [12,14,37-41]. Short-term administration has demonstrated beneficial outcomes, notably superior to those relying solely on diuretics [8,11]. Thus, the premature discontinuation of hydralazine in acute heart failure treatment or cessation of further research into its efficacy might be ill-advised. The adverse effects observed with long-term hydralazine use are most pronounced when administered as monotherapy [41]. Concurrent administration with other pharmacological agents, such as enalapril or isosorbide dinitrate, has shown to reduce these adverse effects substantially [38,42,43]. This synergy suggests potential underexplored benefits of hydralazine in combination therapies. Unfortunately, the negative perceptions stemming from solo hydralazine therapy outcomes [15,19,41] have impeded further investigation into optimal dosages and combinatory efficacy, areas that could potentially redefine its role in heart failure management. Therefore, it is rational to consider continued research and use of hydralazine as part of a combination therapy regime.

Despite the inconsistent effects of hydralazine in the treatment of heart failure caused by various conditions such as coronary artery disease and dilated cardiomyopathy, it has shown promising results in treating heart failure primarily characterized by mitral valve regurgitation [6,11,12,14,31]. This is particularly significant because of the high incidence of mitral valve insufficiency and the predominance of pharmacological treatments in veterinary medicine [1,2]. These factors suggest that further research into hydralazine is warranted, making it a compelling area of study within the field of veterinary cardiology.

Hydralazine in veterinary medicine

During the period when hydralazine was a subject of considerable enthusiasm in human cardiology, veterinary medicine also saw heightened interest in this drug. Significant research into its potential for treating mitral valve insufficiency in animals was initiated, with Mark D. Kittleson leading some of the most pivotal studies in the field [13,26]. Kittleson conducted two major studies on hydralazine. His first paper demonstrated the positive effects of hydralazine in dogs suffering from myocardial failure due to left ventricular ischemia and infarction, thus

establishing its potential as a treatment for heart failure in dogs [13], similar to its use in humans. Building on this, his second study focused on dogs with naturally occurring mitral valve insufficiency at the end-stage of congestive heart failure who were resistant to diuretics. The study found that short-term administration of hydralazine led to a significant decrease in pulmonary wedge pressure by about 35% and improved pulmonary edema in these diuretic-resistant cases [44-47].

Unlike in human medicine, long-term and standalone administration of hydralazine in veterinary medicine has not been thoroughly studied. Despite initial positive findings, it remains unclear why comprehensive large-scale follow-up studies on long-term administration have not been conducted since the 1980s [5]. It is speculated that the numerous side effects and less-than-expected outcomes observed in long-term human trials might have discouraged further research in veterinary settings, especially as the enthusiasm for hydralazine waned following disappointing results in human heart failure treatments [19,27,36,37-39].

Moreover, during the period when hydralazine's popularity began to decline, veterinary medicine saw a surge in interest and research into other treatments for MR, such as ACE inhibitors, spironolactone, pimobenda and diuretics [48-59]. This shift in focus likely contributed to the diminished attention toward hydralazine, as new therapeutic options became more prominent and continued to be explored actively.

Hydralazine: A glimmer of hope in the treatment of mitral valve regurgitation in dogs

Although hydralazine has fallen out of favor in human medicine due to its side effects and questionable long-term efficacy in treating heart failure [19,38,39,60], it is difficult to directly apply these conclusions to veterinary medicine where hydralazine still holds considerable promise.

In veterinary practice, the predominant cause of left-sided congestive heart failure in dogs is mitral valve regurgitation [61]. This condition responds more positively to afterload reduction therapies provided by arterial vasodilators like hydralazine, which can decrease mitral regurgitation volume and subsequently reduce pulmonary wedge pressure, potentially improving heart failure outcomes [6,47]. This contrasts significantly with other causes of left-sided congestive heart failure, making it an appealing option despite the negative findings in human studies. Furthermore, comprehensive and large-scale studies on the long-term effects of hydralazine in veterinary patients with mitral valve regurgitation are still lacking. This scarcity of data makes it challenging to extrapolate the negative long-term outcomes observed in human research directly to veterinary applications.

Additionally, when hydralazine is used in dogs with stage C mitral valve regurgitation as classified by the American College of Veterinary Internal Medicine (ACVIM), it is typically combined with other drugs such as ACE inhibitors, spironolactone, pimobendane, furosemide, and torsemide [3]. It is not yet well understood whether hydralazine's side effects are reduced when used in conjunction with these medications [62]. There are reports in human medicine that suggest combining hydralazine with other cardiac drugs can reduce its associated adverse effects, indicating that its limitations and side effects might be overcome through combination therapy [3,38,62,63]. Therefore, additional research is essential to fully explore the potential benefits and limitations of hydralazine in treating mitral valve regurgitation in veterinary medicine.

Amlodipine in human medicine

Following a period of disillusionment with hydralazine as an afterload reducer in heart failure treatment, interest in arterial vasodilators had significantly waned. However, the emergence of amlodipine, a new calcium channel blocker, reignited interest in the use of arterial vasodilators for heart failure management [23,64]. Unlike other calcium channel blockers, amlodipine, which was introduced in the 1990s, exhibits fewer adverse effects on myocardial contractility [18,23,35,65].

Amlodipine has shown promising results in treating congestive heart failure, similar to those initially expected from hydralazine but without the detrimental impact on heart pump function [23,46,66]. Research involving amlodipine has demonstrated improvements in myocardial contractility indicators, myocardial blood flow, systemic and pulmonary arterial resistance, exercise capacity, and a decrease in plasma catecholamine levels. [66-70]. These beneficial effects have been consistent in both short-term and long-term studies [66]. Moreover, the side effects that often preclude the continuation of drug therapy have been almost non-existent at therapeutic doses, making amlodipine a viable and effective option in heart failure treatment [23,66-69].

Amlodipine in veterinary medicine

In veterinary medicine, significant research has been conducted on amlodipine's effect in treating mitral valve regurgitation, a common cause of congestive heart failure in dogs [20,29,62,70-73]. For example, Suzuki et al. observed a decrease in left atrial pressure in dogs with experimentally induced mitral valve regurgitation treated with amlodipine, a response not seen with benazepril [73]. Similarly, Madron et al. reported that long-term survival benefits were noted when amlodipine was used in combination with furosemide, ACE inhibitors, pimobendane, and spironolactone in dogs with mitral valve regurgitation [57]. They suggested that amlodipine's blood-pressure-lowering effects might activate the RAAS system, but this activation is partially reduced by ACE inhibitors, enhancing survival in these cases.

Furthermore, Park et al. assessed the short-term effects of amlodipine in patients already receiving ACE inhibitors, pimobendane, and spironolactone, exhibited rapid ventricular enlargement [74]. Their findings indicated significant reductions in left ventricular size and E wave flow, underscoring amlodipine's beneficial impact in acute settings. Despite limited studies on amlodipine's effectiveness in treating mitral valve regurgitation, the results have generally been positive, with serious side effects rarely reported [23,46,66]. Issues such as gum swelling and mild increases in renal markers have been noted, but these have not necessitated the discontinuation of treatment [62, 64,75,76].

Nevertheless, the application of amlodipine as a method of reducing afterload in veterinary patients with mitral valve regurgitation remains a minor treatment strategy, with no large-scale collaborative studies currently underway and only moderate interest among veterinary cardiologists. This lack of focus may be attributed to the extensive and active research since the 1980s into other treatments for mitral valve regurgitation, such as ACE inhibitors, spironolactone, pimobendan, and loop diuretics [48–57,77]. These drugs have shown sufficient effectiveness, consuming the limited research funding, time, and personnel available, which might explain why amlodipine has not yet received more intense attention.

In conclusion, while the management of mitral valve regurgitation with major drugs like ACE inhibitors, spironolactone, pimobendane, and loop diuretics is effective, these treatments are not without issues of drug

resistance, and patients continue to succumb to heart failure and its complications [50,77-79]. There is a palpable need among veterinary cardiologists for additional drugs to manage patients who show resistance or non-responsiveness to established major treatments. It is time to focus more on incorporating new drugs like amlodipine into the major league of treatments for mitral valve regurgitation.

Personal experience with the application of hydralazine and amlodipine in canine mitral valve regurgitation

In the field of veterinary medicine, clinical papers exploring the use of hydralazine and amlodipine to treat mitral valve regurgitation in dogs are scarce. Given the limited literature on this topic, I intend to share my personal clinical experiences with these medications. Over the past decade, I have used hydralazine and amlodipine to manage canine mitral valve regurgitation, even though my findings are still in preparation for publication. Despite concurrent treatments with angiotensin-converting enzyme inhibitors, pimobendane, and loop diuretics, I observed significant clinical improvements in dogs classified as ACVIM stage D. When treated with hydralazine at dosages of 0.5-2 mg/kg BID, these dogs showed a dramatic reduction in recurrent heart failure and a decrease in left ventricular end-diastolic diameter. This regimen also led to a reduced need for diuretics and markedly enhanced the patients' quality of life. Severe systemic arterial hypotension or rapid deteriorations in renal function due to decreased GFR were rare. The most common side effects reported by owners were gastrointestinal, particularly decreased appetite.

In cases similarly treated with amlodipine at dosages ranging from 0.2 to 0.6 mg/kg SID, the striking improvements seen with hydralazine were not as pronounced. However, amlodipine administration was associated with a reduced frequency of heart failure recurrence and a slower progression in diuretic dosage, without severe adverse effects. I hope that these observations can be substantiated through more comprehensive research in the future.

SUMMARY

The use of arterial vasodilators as afterload reduction therapy for mitral regurgitation represents a particularly compelling treatment modality in veterinary medicine. Although long-term studies with hydralazine in human research have yielded disappointing results, it is premature to dismiss its applicability in the management of mitral regurgitation in veterinary medicine. There is a pronounced need for more comprehensive and prolonged proactive research in this area. Notably, amlodipine has demonstrated positive outcomes in studies involving humans with congestive heart failure and in veterinary research addressing mitral regurgitation. However, substantial additional research is required before amlodipine can be considered a major recommended pharmacological intervention for mitral valve insufficiency.

CONFLICTS OF INTEREST

None.

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