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Letter to the editor regarding "Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"

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Abstract

The manuscript entitled *Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial*[1] reports a study which sought to answer the question “could pimobendan be all that is needed beyond loop diuretics to manage congestive heart failure (CHF) in myxomatous mitral valve disease (MMVD)?” This was done by prospectively comparing the efficacy of pimobendan + ramipril + furosemide (triple treatment) to pimobendan + furosemide (double treatment) to treat new-onset CHF caused by MMVD.

Disciplines

Small or Companion Animal Medicine | Veterinary Toxicology and Pharmacology

Comments

This article is published as Atkins, Clarke, Bruce Keene, Teresa C. DeFrancesco, Sandra Tou, Valérie Chetboul, Étienne Côté, Stephen Ettinger, Philip R. Fox, Robert L. Hamlin, Jonathan P. Mochel, Jean-Louis Pouchelon, and Rebecca L. Stepien. "Letter to the editor regarding" Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"." *Journal of Veterinary Internal Medicine* (2021). DOI: 10.1111/jvim.16035. Posted with permission.

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LETTER TO THE EDITOR

Letter to the editor regarding "Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"

Dear Editors,

The manuscript entitled *Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial*[1] reports a study which sought to answer the question "could pimobendan be all that is needed beyond loop diuretics to manage congestive heart failure (CHF) in myxomatous mitral valve disease (MMVD)?" This was done by prospectively comparing the efficacy of pimobendan + ramipril + furosemide (triple treatment) to pimobendan + furosemide (double treatment) to treat new-onset CHF caused by MMVD.

While agreeing with the authors that this question has merit, we share several comments and questions regarding applicability of their study results to current practice. During the VALVE trial, worsening signs of CHF were primarily managed with progressively larger diuretic dosages, as opposed to other potential pharmacological interventions such as greater renin-angiotensin-aldosterone system (RAAS) suppression, alternative diuretic use, higher pimobendan dosing, and arterial vasodilator treatment. While the angiotensin-converting enzyme inhibitor (ACEI) ramipril (VASOTOP) was begun at a once daily dosage according to label recommendation, the initial furosemide dosage (median, 8 mg/kg/d), high by current clinical standards, was increased to as much as 15 mg/kg/d, before predefined treatment failure was reached; ramipril dosage was increased (doubled) in only 3 dogs. Spironolactone dosing was left to the clinicians' discretion (added to baseline treatment in only 13 dogs, 8 in the triple treatment group, and 5 dogs in the double treatment group).

The VALVE trial did not assess the efficacy of RAAS suppression using biomarkers. Therefore, the question of whether ramipril adequately or optimally suppressed RAAS, while failing to improve survival in the face of these diuretic dosages, remains unanswered.

We are also concerned that dogs in both treatment groups received ACEI for an average of 9 months before entering the study (44% of triple treatment group vs 26% of double treatment group; P = .02), indicating that over one-quarter of the double treatment group (the no ACEI group) previously had received an ACEI—and for a duration longer than the median 7.6 months that these dogs remained in the study. This is important because it is known that RAAS suppression before the onset of CHF has favorable effects on cardiac remodeling.[2]

Although unknowable by the authors at the time of the VALVE trial design, other studies completed during the 10-year duration of the VALVE trial have demonstrated significant benefit from greater, longer, and more broad-spectrum RAAS suppression (eg, higher or q12h ACEI dosing and mineralocorticoid antagonist [MRA] inclusion) in treating proteinuria and CHF.[3-5]

Because the VALVE trial was performed under Good Clinical Practice guidelines, owner adherence to the trial protocol was quantified. It would be useful to know whether those measurements identified "adherence parity" between the 2 treatment groups, thus eliminating 1 potential source of unintentional bias.

Ramipril, a narrow-spectrum RAAS suppressant (ie, it causes no direct MRA effect), was tested as an "add-on" to drugs providing symptomatic relief (pimobendan and furosemide). Although the absence of an MRA as part of the test article is understandable because of the timing of the VALVE study design, its absence impairs our understanding of the potential role that true RAAS suppression (ie, more RAAS suppression than ACE inhibition alone) might play in managing CHF caused by MMVD. It is now known that incomplete RAAS suppression (aldosterone breakthrough) is common with either ACEI or angiotensin II receptor blockers (ARB) in normal dogs challenged with furosemide or amlodipine[5,6]; with ACEI in natural MMVD before CHF (without furosemide)[5,7]; and in MMVD with CHF in dogs receiving ACEI and furosemide.[5,7] Furthermore, inclusion of MRAs in therapeutic protocols has improved survival in CHF caused by MMVD.[3,5]

Although it has not been directly investigated, it is likely that the high doses of furosemide used in the VALVE Trial, with greater RAAS stimulatory potential, enhanced the propensity for aldosterone breakthrough.[8] In dogs treated with ACEI and ARBs, there is an estimated 30% to 40% incidence of aldosterone breakthrough at conventional furosemide dosages, and a proportional clinical benefit is seen with broad-spectrum RAAS suppression.[3,5-7,9] For this

reason, it would be important to know the average maximum furosemide dosage received, as well as the number of dogs that experienced renal compromise, were euthanized, or exited the study for polyuria and polydipsia or worsening renal dysfunction.

It would also be relevant to know the number of cases accrued from each institution, as well as the average furosemide dosage, number of dogs receiving spironolactone or doubled ramipril dosage, and how these potential institutional differences were accounted for during data analysis. A large number of cases from a single center may diminish the benefits of a multicenter study design or raise the possibility of unintentional institutional acquisition bias.

Although the VALVE results are surprising and interesting, a conclusion that they obviate the need for ACEI treatment in the management of CHF from MMVD is not justified. We believe this study to be hypothesis generating, rather than pivotal. A larger study, employing methodology that provides evidence of more complete RAAS inhibition with contemporary adjunctive heart failure treatment is needed to provide pivotal data upon which to guide practice.

CONFLICT OF INTEREST

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