Acute Effect of Pimobendan and Furosemide on the Circulating Renin-Angiotensin-Aldosterone System in Healthy Dogs

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Background: The renin-angiotensin-aldosterone system (RAAS) is activated in states of decreased cardiac output and by certain cardiovascular therapeutic agents, such as loop diuretics and vasodilators.

Hypothesis: Short-term treatment with the inodilator, pimobendan, will not activate the circulating RAAS because its vasodilatory action will be offset by its positive inotropic property, thereby ameliorating RAAS stimulation at the juxtaglomerular apparatus. Furthermore, pimobendan will suppress RAAS activation produced by furosemide.

Animals: Nine healthy laboratory dogs were used in this study.

Methods: Experimental, cross-over study. Dogs were administered pimobendan (0.5 mg/kg q12h) for 4 days followed by furosemide (2 mg/kg q12h) and then, after a wash-out period, a combination of the drugs. Aldosterone : creatinine (A : Cr) was measured at the end of each treatment cycle.

Results: There was no significant increase in the average urinary A : Cr with the administration of pimobendan (control urinary A : Cr = 0.46, standard deviation (SD) 0.33; pimobendan A : Cr = 0.48, SD 0.28). There was a significant increase in the average urinary A : Cr after administration of furosemide (urinary A : Cr = 1.3, SD 0.70) and with the combination of furosemide and pimobendan (urinary A : Cr = 2.9, SD 1.6).

Conclusions and Clinical Relevance: Short-term administration of high-dose pimobendan, does not activate the RAAS in healthy dogs. Pimobendan did not prevent RAAS activation associated with furosemide therapy. These results in healthy dogs suggest that furosemide therapy, with or without pimobendan, should be accompanied by RAAS suppressive therapy.

Key words: Furosemide; Heart failure; Inodilator; Pimobendan; Renin-angiotensin-aldosterone system.

Abbreviations:
A : Cr aldosterone: creatinine ratio
BP blood pressure
q12h every 12 hours
RAAS renin angiotensin aldosterone system
SD standard deviation
SUN serum urea nitrogen
UA urinalysis

Circulating RAAS activation can be measured by quantification of serum renin, angiotensin II, and aldosterone concentrations or by evaluating urinary aldosterone secretion either by 24-hour urinary aldosterone excretion or by the urinary aldosterone : creatinine ratio (A : Cr). Measuring serum renin, angiotensin, and aldosterone concentrations to evaluate RAAS activation can be problematic because of misleading minute-to-minute variations in serum hormone levels.13 Urinary aldosterone concentrations provide an “average” estimate of aldosterone secretion over several hours as the aldosterone-containing urine pools in the bladder. The urinary A : Cr has been validated and used as an indicator of 24-hour aldosterone secretion.3,13,14

We hypothesized that pimobendan would not activate the RAAS because its positive inotropic effect would maintain renal blood flow, offsetting the vasodilatory tendency to activate the RAAS in healthy animals. Furthermore, we tested the hypothesis that pimobendan might blunt furosemide-induced RAAS activation.

Materials and Methods

The study protocol (Fig 1) was approved by the North Carolina State University Animal Care and Use Committee. On day 0, 9 research dogs (7 females and 2 males, average body weight 19.9...
Fig 1. Time line showing sequence of medications and the tests performed at each point in time. Day 0—physical examination and baseline diagnostics (serum chemistry and electrolytes, complete blood count, and urine A:Cr [am and pm samples mixed]) were gathered. Day 1—Pimobendan administration was initiated and continued for 4 days. Day 4—Pimobendan was administered in the morning, blood was drawn, and morning and evening urine samples were collected, frozen and later mixed for A:Cr determination. The dogs were then allowed a 72-hour wash-out period. On day 7, furosemide administration was begun and continued for 2 days. Blood was then drawn for serum chemistry and electrolyte determination and complete blood count. Morning and evening urine samples were collected, mixed, and frozen, as described above. Pimobendan administration was reinitiated and the combination of furosemide and pimobendan was continued for 3 days, at which time blood was drawn and urine samples were again collected and handled as described. Chemistry, serum chemistry panel; A:Cr, aldosterone: creatinine; UA, urinalysis; BP, blood pressure determination. Treatment (0.5 mg/kg q12h), furosemide (2 mg/kg q12h) and the combination of pimobendan and furosemide. Values for SUN and electrolytes are displayed for all treatment situations dogs receiving pimobendan (0.5 mg/kg q12h), furosemide (2 mg/kg q12h) and the combination of pimobendan and furosemide.

Results

There were no significant abnormalities found on physical examination, complete blood counts, serum chemistry analyses, urinalyses, or blood pressure evaluations. After administration of pimobendan, there was a significant (P < .01) but mild, clinically irrelevant, increase in the mean (SD) serum sodium concentration whereas the combination of furosemide and pimobendan produced a likewise clinically unimportant fall in serum sodium concentration (P < .01; Table 1). Furosemide administration was associated with a decrease in serum potassium concentration (P = < .01; Table 1). The combination of furosemide and pimobendan was also associated with a reduction in serum potassium concent-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SUN (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Phosphorous (mg/dL)</th>
<th>Sodium (mmol/L)</th>
<th>Potassium (mmol/L)</th>
<th>Chloride (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>16.4</td>
<td>0.84</td>
<td>3.8</td>
<td>147.2</td>
<td>4.1</td>
<td>109.9</td>
</tr>
<tr>
<td></td>
<td>(3.13)</td>
<td>(0.21)</td>
<td>(0.73)</td>
<td>(1.39)</td>
<td>(0.28)</td>
<td>(1.45)</td>
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<tr>
<td>Pimobendan</td>
<td>13.6*</td>
<td>0.82</td>
<td>3.6</td>
<td>149.2*</td>
<td>4.0</td>
<td>110.3</td>
</tr>
<tr>
<td></td>
<td>(2.19)</td>
<td>(0.21)</td>
<td>(0.39)</td>
<td>(1.56)</td>
<td>(0.33)</td>
<td>(1.56)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>19.1</td>
<td>0.98*</td>
<td>3.9</td>
<td>147.3</td>
<td>3.6*</td>
<td>104.9*</td>
</tr>
<tr>
<td></td>
<td>(2.98)</td>
<td>(0.29)</td>
<td>(0.21)</td>
<td>(1.80)</td>
<td>(0.48)</td>
<td>(1.80)</td>
</tr>
<tr>
<td>Pimobendan + furosemide</td>
<td>20.9*</td>
<td>0.98*</td>
<td>4.0</td>
<td>144.9*</td>
<td>3.7*</td>
<td>102.7*</td>
</tr>
<tr>
<td></td>
<td>(3.62)</td>
<td>(0.27)</td>
<td>(0.52)</td>
<td>(2.15)</td>
<td>(0.39)</td>
<td>(3.31)</td>
</tr>
<tr>
<td>Normal values</td>
<td>8–27</td>
<td>0.5–1.6</td>
<td>2–6.7</td>
<td>147–154</td>
<td>3.9–5.2</td>
<td>104–117</td>
</tr>
</tbody>
</table>

Control values are those obtained before drug administration. See text for detailed description.

*P < .05, as compared with control values.

SUN, serum urea nitrogen.
tration \( (P < .02) \). Serum chloride concentration fell \( (P < .01; \text{Table 1}) \), with furosemide alone and with the combination of furosemide and pimobendan.

Pimobendan mildly, but significantly \( (P < .05) \), lowered the average serum urea nitrogen (SUN), whereas the administration of furosemide with pimobendan increased both SUN \( (P < .01) \) and serum creatinine concentration \( (P < .05; \text{Table 1}) \). With furosemide alone, a similar increase in serum creatinine concentration was observed \( (P < .05; \text{Table 1}) \). None of these changes were considered to be clinically relevant.

The urinary \( \text{A:Cr} \) after the administration of pimobendan alone was not significantly different than the control value (Fig 2). Furosemide administration was associated with a significant \( (P < .01) \) increase in urinary \( \text{A:Cr} \), and the combination of furosemide and pimobendan was also associated with a significantly increased urinary \( \text{A:Cr} \) \( (P < .01 \) and .004, Fig 3).

**Discussion**

The results of this study suggest that pimobendan, unlike other vasodilators, does not activate the RAAS in healthy dogs. This is likely because of pimobendan’s positive inotropic effect maintaining the glomerular filtration rate, thereby mitigating the drug’s potential vasodilatory activation of the RAAS. Furosemide activated the RAAS (Fig 3). Although concurrent administration of pimobendan did not diminish this RAAS activation (Fig 3) and in fact, RAAS activation continued to rise significantly over study days 9–12, during the time in which pimobendan was administered concurrently. It is possible that the combination of furosemide and pimobendan increased RAAS activation by lowering renal blood pressure caused by the respective additive effects of hypovolemia and vasodilation associated with furosemide and pimobendan administration. Another potential interpretation of this finding is a synergistic effect of furosemide and high-dose pimobendan on RAAS activation in the subacute setting by an unknown mechanism. However, the further increase in urinary \( \text{A:Cr} \) on day 12 (3rd day of pimobendan and furosemide combination therapy) seems more likely because of the additional 3 days furosemide administration. This explanation is supported by the fact that the highest average SUN and serum creatinine concentrations were observed with this combination therapy.

Certain limitations to this study should be pointed out. The study used a small number of dogs, and the duration of the pharmacologic exposure was relatively brief. Doses of pimobendan were higher than the manufacturer’s recommendation \( (0.25–0.6 \text{mg/kg/day}) \). This dosage was chosen to guarantee that, if an effect was present, it would be found, and is consistent with the dosage used in the authors’ clinics in the treatment of refractory heart failure. The dosage chosen proved to be advantageous, as it showed that in the subacute setting, even at higher than recommended dosages in healthy dogs, pimobendan does not activate RAAS and does not suppress furosemide-activated RAAS. Another weakness in the study reported herein is that we evaluated the effects of the medications in healthy dogs, and dogs with heart disease or failure might respond differently. Finally, with the study design used, we were not able to ascertain the time of peak or the duration of RAAS activation with more chronic furosemide administration. Because of this, we cannot explain with certainty the apparent further increase in RAAS activation seen with pimobendan plus furosemide as compared with furosemide alone (Fig 3), and this should be evaluated further.

Despite these limitations, we conclude that pimobendan, when used as a single agent even at high dosages,
does not activate circulating RAAS, as indicated by the lack of an increase in average urinary aldosterone excretion in healthy dogs. RAAS activation is, however, observed in this population with both furosemide alone and combination of furosemide and pimobendan. Although these results should be confirmed in clinical patients, it appears that drugs, which blunt the RAAS (ACE-inhibitors, aldosterone receptor blockers, angiotensin II receptor blockers, and possibly β-blockers, alone or in combination) should be included in the pharmacopea for dogs receiving furosemide, with or without pimobendan.

Footnotes

a Cardell, Sharn Veterinary Inc, Tampa, FL
b Vetmedin, Boehringer Ingelheim, Berkshire, UK
c Package insert, Vetmedin
d Salix, Intervet Canada, Whitby, ON, Canada
e Esoterix Laboratories, Calabasas, CA

Acknowledgments

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References