Evaluation of the Potential for Interaction Between a Metaflumizone–Amitraz Combination and Dexmedetomidine Hydrochloride in Dogs*

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This study investigated the effects on cardiovascular parameters, if any, of a commercially available combination of metaflumizone and amitraz administered to healthy, telemetered beagles that were subsequently sedated with dexmedetomidine. Dogs were sedated first without any pretreatment and then after pretreatment with metaflumizone and amitraz. Baseline values of all parameters were within normal limits for all dogs before the first anesthetic event. At 10 and 20 minutes after onset of sedation, oxygen saturation as measured by pulse oximetry was significantly higher for dogs that were pretreated with metaflumizone and amitraz. At all times after induction of sedation, blood pressure, heart rate, and baseline body temperature for dogs pretreated with metaflumizone and amitraz were not statistically different from when they were not pretreated. In conclusion, prior treatment with metaflumizone and amitraz did not influence the hemodynamic response to dexmedetomidine in telemetered dogs.

INTRODUCTION

A commercial combination of metaflumizone and amitraz for topical administration as an ectoparasiticide for dogs (ProMeris for dogs, Fort Dodge Animal Health) was recently approved for the US market. Some clinicians have theorized that amitraz could potentially interact with compounds that have $\alpha_2$-adrenergic agonist activity if it were systemically absorbed following dermal application, even though no actual report of interaction between the metaflumizone–amitraz combination and $\alpha_2$-adrenergic agonists was found in the published literature. Although previously published pharmacokinetic data\(^1\) indicate that transdermal absorption of amitraz is unlikely,
Dexmedetomidine, a potent $\alpha_2$-adrenergic agonist, was recently approved as a sedative and analgesic in dogs and cats to facilitate clinicalexaminations, clinical procedures, minor surgical procedures, and minor dental procedures.\textsuperscript{9–11} It is also indicated for use as a preanesthetic in dogs prior to general anesthesia.\textsuperscript{11} The selection of dexmedetomidine for this study was made based on itscomparatively high selectivity for $\alpha_2$-adrenergic receptors.\textsuperscript{12}

The similarity between octopaminergic receptors in invertebrates and $\alpha_2$-adrenergic receptors in vertebrates has led some investigators to suggest that the formamidines may interfere with specific membrane receptors in vertebrates as well.\textsuperscript{13} Binding studies have demonstrated, in fact, that these compounds can show a weak interaction with $\alpha_2$-adrenergic receptors.\textsuperscript{14,15}

$\alpha_2$-Adrenergic sedatives such as xylazine, detomidine, medetomidine, and dexmedetomidine are frequently administered in veterinary practice. It was theorized that amitraz, when given systemically to mammals, would bind with $\alpha_2$-receptors, producing sedative effects\textsuperscript{16} that may exacerbate the effects of $\alpha_2$-sedatives. This study was designed to investigate the cardiovascular effects, if any, of a topical metaflumizone–amitraz combination administeredcutaneously to telemetered dogs that were subsequently sedated with dexmedetomidine hydrochloride (Dexdomitor, Pfizer Animal Health).
MATERIALS AND METHODS

Animal Care and Instrumentation

The study was approved by the Institutional Animal Care and Use Committee of the testing facility. Seven healthy, sexually intact beagles (four males and three females; age range, 18.5 to 31 months; weight range, 9.8 to 12.4 kg) were the subjects of this study. Each dog was equipped with a telemetry device (DSI PhysioTel D70-PCT transmitter, Data Sciences International, Saint Paul, MN) that had been surgically implanted 2 months before the study began. The telemetry device permitted the simultaneous and continuous monitoring of respiratory rate, electrocardiography (ECG), arterial (femoral artery) blood pressure, and body temperature.

Experimental Design

The study was conducted in seven healthy beagles as a single cohort, with each dog serving as its own control. Each dog was sedated with dexmedetomidine hydrochloride twice (3 days apart), first without any pretreatment (control, day 0) and subsequently after being treated with metaflumizone–amitraz (day 3). Topical metaflumizone–amitraz was administered 2 days after the initial anesthetic event (day 2), approximately 24 hours before the second anesthetic procedure. The timing for the second anesthetic event was selected to allow the ectoparasiticide product to distribute throughout the dogs’ haircoat. Temperature, heart rate (HR), respiratory rate, blood pressure, and an estimation of oxygen saturation of hemoglobin as measured by pulse oximetry (SpO₂) were monitored continuously (DSI PhysioTel D70-PCT transmitter; and Passport 2, Datascope, Montvale, NJ). Heating pads (T/Pump, Gaymar Industries Inc., Orchard Park, NY) and hot water blankets were used during anesthesia to maintain body temperature between 37.5°C and 38.5°C.

Statistical Analysis

Data are reported as the mean ± SD. Using the PROC MIXED Procedure (SAS 8.2, SAS Institute, Cary, NC), each parameter was analyzed by a repeated measures analyses of variance with a model that considered treatment as a fixed effect and time as the repeated factor. Treatment was tested with the residual error at the 5% level of significance. Least squares means of the data were calculated for each treatment group. Because the animals served as their own controls, the repeated measures analysis of variance F-test was used to provide the two-sided test to determine whether differences existed between treatments at the 5% level of significance.

Experimental Procedures

Dogs were fasted for 12 hours and water was withheld for 2 hours before dexmedetomidine was administered. A venous catheter was placed in a cephalic vein for administration of dexmedetomidine. Sedation was induced by bolus IV administration of the recommended dose (375 µg/m²) of dexmedetomidine given over approximately 60 seconds, in accordance with label directions. Once dexmedetomidine was administered, the dosing syringe was removed from the catheter, the catheter was flushed with saline, and auffed tracheal tube was placed. However, at no time during the experiments was there a need to mechanically ventilate the lungs because no sedation-induced apnea was observed.

During each of the two anesthesia events, the ECG; HR (bpm); systolic (SAP), diastolic (DAP), and mean (MAP) arterial pressures (mm Hg); end-tidal isoflurane and carbon dioxide concentrations (ETISO and ETCO₂, respectively); SpO₂ (%); and body temperature (°C) were monitored continuously (DSI PhysioTel D70-PCT transmitter; and Passport 2, Datascope, Montvale, NJ). Heating pads (T/Pump, Gaymar Industries Inc., Orchard Park, NY) and hot water blankets were used during anesthesia to maintain body temperature between 37.5°C and 38.5°C.
RESULTS
Baseline values for HR, SpO₂, MAP, SAP, and DAP were within normal limits for all dogs before the first anesthetic event. Baseline HR was slightly lower (not statistically significant) in dogs pretreated with the metaflumizone–amitraz combination, but HRs became similar to those in untreated dogs within 10 minutes after dexmedetomidine administration (Figure 1). All parameters were similar for all times (10 to 60 minutes) after dexmedetomidine administration in dogs pretreated with metaflumizone–amitraz except for two time points, 10 and 20 minutes after the onset of sedation, at which times SpO₂ was significantly higher (Table 1).

DISCUSSION
Beagles have become a major model for use in pharmacologic safety studies, which are required by the International Conference on Harmonisation “Guidelines on Safety Pharmacology” (ICH S7A) finalized by the FDA in 2001. Cardiac electrophysiology in these dogs plays a decisive role in the selection of a potential “cardio-safe” new chemical entity. Telemetry is a well-researched and validated method to study variations in hemodynamic parameters in beagles, and the use of telemetry in the dogs in this study facilitated continuous, sensitive, precise, and repeatable measurements of such physiologic parameters as HR, MAP, SAP, and DAP.

The interaction between amitraz and dexmedetomidine in mammals was theorized based on the understanding that the binding pattern of these compounds may overlap owing to the structural similarities of octopaminergic and adrenergic receptors. To date, there have been no reports of an actual clinical interaction between these compounds. This may be related to the lower affinity of amitraz to mammalian receptors and/or the fact that amitraz is not systemically absorbed after topical administration.

Because of the similarity of octopaminergic and α₂-receptors, oral administration of amitraz can produce a sedative effect accompanied by lower HR and body temperature. Although baseline HR was lower (albeit not significantly different) when dogs were pretreated with metaflumizone–amitraz compared with when they were not pretreated, it is unlikely...

Figure 1. Heart rate before (baseline) and after induction of anesthesia with dexmedetomidine either under control conditions or 24 hours after treatment with metaflumizone–amitraz.
that this effect can be attributed to amitraz because body temperature was not decreased and there was no sign of sedation. These measurements were taken 3 days apart, and HR may have been influenced by the behavioral state of the dogs. Also, the relatively small sample size of this study might be a contributing factor. It is noticeable that immediately after induction of anesthesia, HRs were similar for pretreated and non-pretreated dogs.

The results demonstrate that the administration of the highly selective \(\alpha_2\)-agonist dexmedetomidine to dogs that have been treated with this combination of metaflumizone and amitraz does not produce adverse side effects as investigated in this study. Values for HR, temperature, and mean SAP and DAP after the administration of dexmedetomidine in dogs that had been pretreated with the metaflumizone–amitraz combination were not different \((P > .05)\) than when the dogs were not pretreated. SpO\(_2\) was significantly higher at 10 and 20 minutes after onset of anesthesia in the dogs pretreated with metaflumizone–amitraz; however, the difference was small and very likely to be clinically irrelevant.

**TABLE 1. Hemodynamic Parameters before (Baseline) and after Anesthesia Induction with Dexmedetomidine under Either Control Conditions or 24 Hours after Receiving Topical Treatment with a Combination of Metaflumizone and Amitraz**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
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<tr>
<td><strong>HR (bpm)</strong></td>
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<td></td>
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<tr>
<td>CTRL</td>
<td>94 ± 6</td>
<td>72 ± 7</td>
<td>54 ± 3</td>
<td>57 ± 3</td>
<td>55 ± 4</td>
<td>55 ± 5</td>
<td>54 ± 6</td>
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<tr>
<td>M + A</td>
<td>76 ± 5</td>
<td>68 ± 6</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
<td>64 ± 8</td>
<td>54 ± 3</td>
<td>63 ± 8</td>
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<td><strong>SpO(_2) (%)</strong></td>
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<td></td>
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<tr>
<td>CTRL</td>
<td>93 ± 1</td>
<td>87 ± 2</td>
<td>91 ± 2</td>
<td>94 ± 1</td>
<td>93 ± 2</td>
<td>94 ± 2</td>
<td>95 ± 2</td>
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<tr>
<td>M + A</td>
<td>94 ± 1</td>
<td>92* ± 1</td>
<td>96* ± 1</td>
<td>94 ± 0</td>
<td>95 ± 1</td>
<td>95 ± 1</td>
<td>94 ± 1</td>
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<td><strong>MAP (mm Hg)</strong></td>
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<tr>
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<td>119 ± 5</td>
<td>148 ± 9</td>
<td>130 ± 8</td>
<td>117 ± 8</td>
<td>112 ± 6</td>
<td>108 ± 6</td>
<td>106 ± 6</td>
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<td>136 ± 7</td>
<td>128 ± 6</td>
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<td>115 ± 6</td>
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<td><strong>SAP (mm Hg)</strong></td>
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<tr>
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<td>189 ± 11</td>
<td>165 ± 9</td>
<td>155 ± 9</td>
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<tr>
<td>CTRL</td>
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<td>127 ± 8</td>
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<td><strong>Body temperature (ºC)</strong></td>
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<tr>
<td>M + A</td>
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<td>38 ± 1</td>
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</table>

*Statistically significant difference \((P < .05)\) from control.

CTRL = control; DAP = diastolic arterial pressure; HR = heart rate; M + A = metaflumizone and amitraz; MAP = mean arterial pressure; SAP = systolic arterial pressure; SpO\(_2\) = oxygen saturation as measured by pulse oximetry.
CONCLUSION

Prior treatment (24 hours) with a combination of metaflumizone and amitraz did not influence the hemodynamic response to dexmedetomidine in telemetered dogs. This confirms the safety of using an α₂-adrenergic agonist, such as dexmedetomidine, for anesthetizing dogs previously treated with this commercially available combination of metaflumizone and amitraz.

ACKNOWLEDGMENTS

We thank Dr. Carlos del Rio, DVM, PhD, for scientific support and Deborah Amodie, BS, for statistical analysis.

REFERENCES