Medetomidine acts primarily as an agonist at alpha-2 adrenoreceptors in the central and peripheral nervous systems. In addition to inducing reliable sedation and analgesia, alpha-2 agonists such as medetomidine have many desirable clinical effects, including:

- Their ability to be delivered through various routes of administration (eg, IM, IV bolus or CRI, epidural, transmucosal)
- Their ability to work synergistically with other types of sedatives (eg, opioids, phenothiazines, benzodiazepines) to induce sedation, analgesia, and immobility
- Their ability to contribute to balanced anesthesia by significantly reducing the required doses of inhalant and injectable anesthetics
- Their ability to be antagonized (reversed) with alpha-2 antagonists such as atipamezole

Although alpha-2 agonists are important sedative drugs in veterinary medicine, their use is often limited by their adverse effects and perceived complication risk, because, in addition to their desirable CNS effects, they interact with receptors outside the CNS, including the cardiovascular system, GI tract, and endocrine system. These potential adverse effects are often what practitioners consider when deciding whether and how to use alpha-2 agonists.

Alpha-2 agonists can cause significant cardiovascular alterations via 2 main mechanisms: increased peripheral vascular resistance and decreased sympathetic outflow from the brain. The peripheral vasoconstriction that follows administration activates a baroreceptor reflex that decreases heart rate (ie, reflex bradycardia), which is a protective reflex that reduces workload on the heart. Central effects of alpha-2 agonists include lowered blood pressure and heart rate, although these result from a mechanism other than the baroreceptor reflex.

Due to the relatively complex cardiovascular effects of alpha-2 agonists, veterinarians may choose to avoid using them in dogs altogether. Unfortunately, this means that many dogs may
not benefit from their sedative and analgesic effects for a range of procedures, including physical examinations, diagnostic imaging, and minor surgical procedures; thus, extensive research has been conducted over the last 10 to 15 years to find ways to lessen the cardiovascular effects of alpha-2 agonists so practitioners can feel more comfortable using them across a wider cross-section of patients and more animals can benefit from their use.

One exciting recent development has been the discovery and evolving use of the peripherally acting alpha-2 antagonist, vatinoxan.1-4 Vatinoxan does not cross the blood–brain barrier and therefore does not affect the level of sedation or analgesia induced by medetomidine.2,5 After being absorbed from the injection site, vatinoxan binds to peripheral alpha-2 receptors on blood vessels, blunting the vasoconstrictive effects of medetomidine at these sites. By combining medetomidine with vatinoxan in the same IM injectable solution, sedation can be achieved with fewer of the typical alpha-2 agonist-associated cardiovascular effects (ie, less hypertension and bradycardia).4,6 Vatinoxan has been formulated in combination with medetomidine to create a novel option for procedural sedation in dogs in many parts of the world.

The Study
A recent single-site, blinded, randomized, crossover study investigated the cardiovascular effects of using either IM medetomidine (MED) or a combination of medetomidine and vatinoxan (MVX) in dogs.4 The primary objective was to compare the major cardiovascular effects of the 2 sedation protocols, with a difference in cardiac output of ≥20% between the 2 treatment groups being clinically relevant. A secondary objective was to describe whether relative changes in heart rate could be used to predict relative changes in cardiac output in clinical practice settings when cardiac output cannot readily be measured.

Dogs were evaluated for a variety of cardiovascular and respiratory parameters; after baseline measurements were taken, either the recommended label dose of MVX (1 mg m⁻² medetomidine and 20 mg m⁻² vatinoxan) IM or an equivalent dose of MED IM was administered based on the randomization protocol. Based on dog size, these doses represent a dosing range of 0.04–0.05 mg kg⁻¹ of medetomidine. Data were collected at predetermined intervals from baseline over 120 minutes. No assessments of sedation or analgesia were performed so as not to interfere with the cardiovascular measurements.

The cardiovascular parameters measured included heart rate (HR), stroke volume (SV), cardiac output (CO), systemic and pulmonary blood pressures (BP), systemic and pulmonary vascular resistance (SVR and PVR), arterial oxygenation content, oxygen delivery, oxygen consumption, and oxygen extraction ratio.

Although many of these parameters are not readily monitored in a clinical setting, they allow for a better understanding of the effects of these drug combinations and whether MED or MVX can be safely administered to a particular canine patient.

The results demonstrated that MED resulted in more vasoconstriction (resulting in greater SVR and PVR values), higher systemic and pulmonary BPs, lower SV, and lower HR as compared with patients receiving MVX for the entire observation period. CO in patients receiving MED was 47% to 96% lower than in those receiving MVX, reflecting a significant difference between groups (p <0.0001). Looking at individual treatments over time, dogs receiving MED had COs reduced to 23% to 30% of their baseline values for the entire observation period, whereas CO in dogs receiving MVX was reduced to 50% to 58% of their baseline CO for the first 15 minutes before values trended back up towards baseline over the remainder of the observation period. As the authors stated, a key takeaway of the study is that, even though blood pressure was well maintained after administration of MED, other important parameters (eg, SV, CO) were severely reduced.

More dogs showed signs of arrhythmia in the MED group (sinus arrhythmia, atrioventricular block, and ventricular escape beats) than did dogs receiving MVX. Arterial oxygen saturation was acceptable in both groups, with SaO2 being >90% on room air throughout the 2-hour observation period. However, in the MED group, mixed venous blood samples collected from the pulmonary artery, which can indicate whether CO and oxygen delivery are adequate, demonstrated lower hemoglobin oxygen saturation and oxygen content and higher lactate levels. These changes reflect significantly lower oxygen delivery and higher oxygen extraction following MED administration as compared with MVX, which are consequences of the significant decreases in CO as described above.

Finally, in terms of the secondary outcome of the study, the effects of MED on HR were virtually identical to its effects on CO. This makes sense knowing that CO is the product of HR × SV. This relationship between HR and CO was found to be linear, with relative changes in HR being reflected in similar relative changes in CO (eg, a 50% decrease in HR would equate approximately to a 50% decrease in CO).

Implications for Practice
There are several key findings from this study that can help direct how labeled doses of MVX should be used for sedation in canine patients. Firstly, cardiovascular function is better maintained following MVX than if equivalent doses of MED were used in dogs for sedation purposes. Although only cardiac rhythm, HR, BP, and oxygen saturation can typically be monitored in most practice settings, it is important to recognize that other...
variables are changing in dynamic fashion over time, sometimes severely, and that these changes can have detrimental effects on a patient’s homeostasis, despite having what many would consider to be normal to slightly high (ie, “acceptable”) blood pressure.

Establishing that there is a linear relationship between HR and CO across the range of expected values (eg, a 20% decrease in HR from baseline will result in a corresponding 20% decrease in CO) means that a patient’s HR can be used to help predict what is happening to its CO, which is not necessarily the case with other sedative combinations. Knowing this, an informed decision can be made regarding whether to use an alpha-2 agonist in a particular patient.

Although the study was well designed, a few limitations should be considered before applying its findings to clinical situations. The study only looked at the effects of using a single dose of MED and MVX under specific conditions in dogs (single breed, similar size, controlled laboratory setting). Furthermore, cardiovascular effects could not be correlated with levels of sedation or analgesia, as assessment of these parameters was not performed. Caution should be used when extrapolating these results to clinical scenarios in which patients might be undergoing procedures with a range of stimulation.

Finally, the effects of MVX in dogs with valvular heart disease and/or those being treated with cardiovascular drugs (eg, vasodilatory, sympatholytic, negative chronotropic or inotropic effects), its use IV, and use in combination with other sedatives or followed by injectable or inhalant anesthetics was not assessed in this study and should be further investigated.

Although there is still much to learn regarding procedural sedation in dogs, MVX is an exciting option that can be confidently used at label doses in canine patients for sedation, knowing that its cardiovascular effects will be better than if an equivalent dose of MED was used alone.

**EXPERT COMMENTARY**

The study by Joerger and colleagues is a great addition to our collective knowledge regarding the use of alpha-2 agonists in dogs. It was a very well-designed and conducted study, and the results and conclusions are clinically relevant and applicable to what those of us in small animal practice see and do every day. We are constantly challenged to balance our needs for sedation and analgesia with the need to keep patient physiology as close to normal as possible, and using Zenalpha® (medetomidine and vatinoxan hydrochlorides) for sedation in dogs gets us one step closer to meeting this objective.

**References**


**IMPORTANT SAFETY INFORMATION**

As with all drugs, side effects may occur. For use in dogs only. Not intended for use in cats. Not for use in humans. Avoid skin, eye or mucosal contact. In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician. DO NOT DRIVE as sedation, loss of consciousness, and changes in blood pressure may occur. People with cardiovascular disease and pregnant women should exercise special caution to avoid exposure. Uterine contractions and decreased fetal blood pressure may occur after accidental systemic exposure. As with all alpha-2 adrenergic receptor agonists, onset of sedation may be delayed or may be inadequate in some dogs. Do not use Zenalpha in dogs with cardiac disease, respiratory disorders, shock, severe debilitation, that have hypoglycemia or are at risk of developing hypoglycemia, or are stressed due to extreme heat, cold or fatigue. Zenalpha should not be administered in the presence of pre-existing hypotension, hypoxia or bradycardia. Due to the pronounced cardiovascular effects of alpha2-adrenoceptor agonists, only clinically healthy dogs (American Society of Anesthesiologists [ASA] classes I and II) should be administered Zenalpha. Dogs should be monitored frequently during sedation for changes in heart rate, blood pressure, respiratory rate and body temperature. Tachycardia may occur in some dogs after recovery from sedation. The following adverse reactions have been reported: diarrhea, muscle tremors and colitis. Refer to the prescribing information on the next page for complete details or visit www.dechra-us.com.
Zenalpha® (medetomidine and vatinoxan hydrochlorides injection) 0.5 mg/mL and 10 mg/mL
For intramuscular injection in dogs only
Sedative, Analgesic

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Zenalpha is a combination of medetomidine and vatinoxan hydrochlorides. Medetomidine is a racemic mixture containing the active enantiomer, medetomidine, an alphadrenoceptor agonist associated with sedative and analgesic properties. Medetomidine is a peripherally selective alpha2-adrenoceptor agonist, which partially counters the cardiovascular depressive effects of medetomidine at peripheral alpha-2-adrenoceptors, while preserving the centrally mediated sedative and analgesic effects of medetomidine.

Vatinoxan hydrochloride has the chemical name (S)-5-(3,3-dimethylbutyl)-1H-imidazo[4,5-f]quinoline-2,4(3H)-dione (3'-e) ethyl methanesulfonfyl hydrochloride. It is a white to pale yellow, crystalline substance, sparingly soluble in water and having a molecular weight of 456 g/mol. The molecular formula is C11H10NO2.HCl and the structural formula is:

\[
\text{C}_11\text{H}_{10}\text{NO}_2\cdot\text{HCl}
\]

Each mL of Zenalpha contains 0.5 mg medetomidine hydrochloride, 10 mg vatinoxan hydrochloride, 0.325 mg mannitol (USP), 4.16 mg citric acid monohydrate (USP), 1.8 mg methylparaben (MF), 0.2 mg propylparaben (MF).

INDICATIONS:
Zenalpha is indicated for use as a sedative and analgesic in dogs to facilitate clinical examination, clinical procedures and minor surgical procedures.

Zenalpha is not intended for use in cats (see Animal Safety Warnings).

Dosage and Administration:
The dose is based on body weight (see Table 1). Calculate the dose using 1 mg medetomidine/10 kg BSA or use the dosing table below. Note that the mg/kg dose decreases as body weight increases.

| Body weight | mg/kg | mL/kg
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>4.4 to 7</td>
<td>2 to 3</td>
<td>0.3</td>
</tr>
<tr>
<td>7.3 to 9</td>
<td>2 to 3</td>
<td>0.5</td>
</tr>
<tr>
<td>9.1 to 11</td>
<td>4 to 5</td>
<td>0.6</td>
</tr>
<tr>
<td>11.2 to 12.5</td>
<td>4 to 5</td>
<td>1.0</td>
</tr>
<tr>
<td>13.5 to 15</td>
<td>5 to 6</td>
<td>1.2</td>
</tr>
<tr>
<td>15.1 to 17.5</td>
<td>6 to 7</td>
<td>1.3</td>
</tr>
<tr>
<td>17.6 to 20.1</td>
<td>7 to 8</td>
<td>1.6</td>
</tr>
<tr>
<td>20.1 to 25.4</td>
<td>7 to 8</td>
<td>1.6</td>
</tr>
<tr>
<td>25.4 to 30.5</td>
<td>7 to 8</td>
<td>1.6</td>
</tr>
<tr>
<td>30.5 to 36.2</td>
<td>7 to 8</td>
<td>1.6</td>
</tr>
<tr>
<td>36.2 to 43.2</td>
<td>7 to 8</td>
<td>1.6</td>
</tr>
<tr>
<td>43.2 to 100</td>
<td>7 to 8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

After administration of Zenalpha, the dog should be allowed to rest quietly until evidence of sedation has occurred (5-15 minutes). The average duration of sedation is 30 minutes. After which, the drug is rapidly metabolized and excreted.

Reversal of Zenalpha:
Administration of IM atipamezole hydrochloride at the approved dose to reverse IM medetomidine hydrochloride results in reversal of the sedative and cardiovascular effects of Zenalpha. Reversal of Zenalpha occurs within 5-10 minutes after administration of atipamezole hydrochloride.

CONTRAINDICATIONS:
Do not use Zenalpha in dogs with cardiac disease, respiratory disorders, shock, severe dehydration, that have hypoglycemia or are at risk of developing hypoglycemia, or are stressed due to extreme heat, cold or fatigue.

Zenalpha is contraindicated in dogs with a known sedative or hypnotic effect.

WARNINGS:
Human User Safety Warnings
Not for use in humans. Keep this and all medications out of reach of children and pets.

Avoid skin contact, eye contact, or inhalation. Wash hands with soap and water and wash and remove contaminated clothing. In a skin irritation occurs, seek the advice of a physician.

In case of accidental oral intake or self-injection, seek medical advice immediately and show the package insert to the physician. DO NOT inject vedolizumab as sedation, loss of consciousness, and changes in blood pressure may occur.

Persons with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid exposure to this product.

Pregnant women should experience special caution to avoid exposure. Urinary tract and cardiovascular system may occur after accidental exposure. Persons with known hypersensitivity to any of the ingredients should avoid contact with Zenalpha. Caution should be exercised when handling sedated animals. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be habituated.

Zenalpha contains medetomidine, an alpha-, alpha-adrenoceptor agonist with direct effects on the cardiovascular system. By limiting its effects to peripheral organ systems, Zenalpha provides sedative and analgesic effects without sedation and analgesia. Although Zenalpha may reduce cardiovascular parameters when compared to baseline parameters in dogs, it is not intended to sedate or render the animal unconscious.

Note to physician: Zenalpha contains medetomidine, an alpha-, alphadrenoceptor agonist with direct effects on the cardiovascular system. By limiting its effects to peripheral organ systems, Zenalpha provides sedative and analgesic effects without sedation and analgesia. Although Zenalpha may reduce cardiovascular parameters when compared to baseline parameters in dogs, it is not intended to sedate or render the animal unconscious.

Zenalpha is intended for use in cats. The use of Zenalpha in cats has been associated with hypotension.

PRECAUTIONS:
Do not use Zenalpha in cats (see Animal Safety Warnings).

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