A CLINICIAN'S BRIEF SUPPLEMENT

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ClinicalApplications

The Cardiovascular Impact of Medetomidine–Vatinoxan versus Medetomidine Alone

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Key Takeaways

- In a study evaluating the effects of medetomidine–vatinoxan (MVX) versus medetomidine (MED) in dogs, cardiovascular function was closer to normal in dogs receiving MVX for all measured parameters as compared with dogs receiving MED.
- Although blood pressure increased over baseline after MED administration and remained within an "acceptable" range, heart rate, stroke volume, cardiac output, and perfusion were reduced after MED administration as compared with MVX administration.
- Heart rate is closely related to cardiac output after administration of either MED or MVX and can be used to guide clinical decision-making.

THE STUDY

Joerger FB, Wieser ML, Steblaj B, Niemann L, Turunen H, Kutter AP. Evaluation of cardiovascular effects of intramuscular medetomidine and a medetomidine–vatinoxan combination in beagle dogs: a randomized blinded crossover laboratory study. *Vet Anaesth Analg*. 2023;50(5):397-407.

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.[1-3] 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.[1] The peripheral vasoconstriction that follows administration activates a baroreceptor reflex that decreases heart rate (ie, reflex bradycardia),[2] 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.[1]

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

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6. Restitutti F, Kaartinen MJ, Raekallio MR, et al. Plasma concentration and cardiovascular effects of intramuscular medetomidine combined with three doses of the peripheral alpha2-antagonist MK-467 in dogs. *Vet Anaesth Analg*. 2017;44(3):417-426.

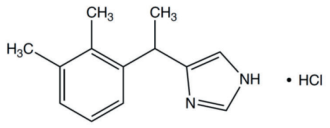
Zenalpha®

(medetomidine and vatinoxan hydrochlorides injection)
0.5 mg/mL and 10 mg/mL
For intramuscular injection in dogs only
Sedative, Analgesic

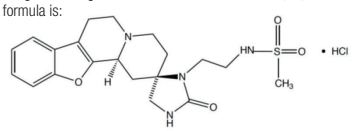
CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Zenalpha is a combination of medetomidine and vatinoxan hydrochlorides. Medetomidine is a racemic mixture containing the active enantiomer, dexmedetomidine, an alpha$_2$-adrenoceptor agonist with sedative and analgesic properties. Vatinoxan is a peripherally selective alpha$_2$-adrenoceptor antagonist, which partially counteracts the cardiovascular depressive effects of dexmedetomidine at peripheral alpha$_2$-adrenoceptors, while preserving the centrally mediated sedative and analgesic effects of dexmedetomidine.

Medetomidine hydrochloride has the chemical name (S,R)-4-[1-(2,3-dimethylphenylethyl)-1H-imidazole hydrochloride. It is a white, crystalline, water soluble substance having a molecular weight of 237 g/mol. The molecular formula is $C_{13}H_{16}N_2$ HCl and the structural formula is:



Vatinoxan hydrochloride has the chemical name N-(2-((2R,12bS)-2'-oxo-1,3,4,6,7,12b-hexahydrospiro[benzofuro[2,3-a] quinolizine-2,4'-imidazolidine]-3'-yl) ethyl) methane sulfonamide hydrochloride. It is a white to pale yellow, crystalline substance, sparingly soluble in water and having a molecular weight of 455 g/mol. The molecular formula is $C_{20}H_{26}N_4O_4S$ HCl and the structural formula is:



Each mL of Zenalpha contains 0.5 mg medetomidine hydrochloride, 10 mg vatinoxan hydrochloride, 32.5 mg mannitol (USP), 4.16 mg citric acid monohydrate (USP), 1.8 mg methylparaben (NF), 0.2 mg propylparaben (NF).

INDICATION:
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 surface area (BSA). Calculate the dose using 1 mg medetomidine /m^2 BSA or use the dosing table below. **Note that the mg/kg dosage decreases as body weight increases.**

Table 1. IM dose volume based on body weight

Dog body weight		Dose volume
lbs	kg	mL
4.4 to 7	2 to 3	0.3
7.1 to 9	3.1 to 4	0.4
9.1 to 11	4.1 to 5	0.6
11.1 to 22	5.1 to 10	0.8
22.1 to 29	10.1 to 13	1.0
29.1 to 33	13.1 to 15	1.2
33.1 to 44	15.1 to 20	1.4
44.1 to 55	20.1 to 25	1.6
55.1 to 66	25.1 to 30	1.8
66.1 to 73	30.1 to 33	2.0
73.1 to 81	33.1 to 37	2.2
81.1 to 99	37.1 to 45	2.4
99.1 to 110	45.1 to 50	2.6
110.1 to 121	50.1 to 55	2.8
121.1 to 132	55.1 to 60	3.0
132.1 to 143	60.1 to 65	3.2
143.1 to 154	65.1 to 70	3.4
154.1 to 176	70.1 to 80	3.6
>176	>80	3.8

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 38 minutes. As with all alpha$_2$-adrenoceptor agonists, onset of sedation may be delayed or may be inadequate in some dogs.

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 sedation occurs within 5-10 minutes after administration of atipamezole hydrochloride.

CONTRAINDICATIONS:
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 is contraindicated in dogs with a known sensitivity to medetomidine or vatinoxan.

WARNINGS:
Human User Safety Warnings

Not for use in humans. Keep this and all medications out of reach of children and pets.

Avoid skin, eye or mucosal contact. Use caution while handling and using filled syringes. Absorption of the active ingredients is possible following exposure via the skin, eye or mucosa. In case of accidental eye exposure, flush eyes with water for 15 minutes, remove contact lenses then continue to flush. In case of accidental skin exposure, wash with soap and water and remove contaminated clothing. If symptoms occur, 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 DRIVE 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 any exposure to this product.

Pregnant women should exercise special caution to avoid exposure. Uterine contractions and decreased fetal blood pressure may occur after accidental systemic 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 heavily sedated.

Note to physician: Zenalpha contains medetomidine, an alpha$_2$-adrenoceptor agonist, in combination with vatinoxan, a peripherally selective alpha$_2$-adrenoceptor antagonist. Symptoms after absorption or accidental self-injection may include dose-dependent sedation, respiratory depression, bradycardia, tachycardia, and hypotension.

Animal Safety Warnings
Zenalpha should not be administered in the presence of pre-existing hypotension, hypoxia or bradycardia. Due to the pronounced cardiovascular effects of alpha$_2$-adrenoceptor agonists, only clinically healthy dogs (American Society of Anesthesiologists [ASA] classes I and II) should be administered Zenalpha. Dogs should be monitored frequently for cardiovascular function and body temperature during sedation.

Zenalpha is not intended for use in cats. The use of Zenalpha in cats has been associated with hypotension.

PRECAUTIONS:
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.

In the event of hypoxia or apnea, supplemental oxygen should be administered.

Following administration of Zenalpha, a decrease in body temperature may occur and an external heat source may be needed to maintain body temperature. Hypothermia may persist longer than sedation and analgesia.

The analgesic effect of Zenalpha will not last longer than the sedative effects. Additional analgesic(s) should be administered as needed (see Effectiveness).

Nervous, excited or agitated dogs with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to Zenalpha (ineffectiveness). The onset of sedative/analgesic effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. Therefore, allow the dog to rest quietly for 10 to 15 minutes after injection.

With the alpha$_2$-adrenoceptor agonist drug class, including Zenalpha, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation) exists.

Repeat dosing with Zenalpha has not been evaluated.

Zenalpha has only been evaluated in fasted dogs; therefore, the effects on fed dogs (for example occurrence of vomiting) has not been characterized.

The concurrent use of anticholinergic medications and Zenalpha has not been evaluated.

Zenalpha may decrease serum glucose in healthy dogs and this effect may persist longer than sedation (see Animal Safety).

The safe use of Zenalpha in dogs with hepatic or renal impairment has not been evaluated.

The safe use of Zenalpha has not been evaluated in dogs younger than 4.5 months old.

The safe use of Zenalpha has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS:
In the field study safety evaluation, 110 dogs received Zenalpha and 113 dogs received dexmedetomidine (control group) for sedation. Dogs ranged in age from 5 months to 14.5 years, weighed 5.1 to 154 lbs, and represented purebreds and breed mixes.

Table 2. Adverse reactions during the field study

Adverse Reaction	Zenalpha (N = 110) n (%)	Dexmedetomidine (N = 113) n (%)
Diarrhea	4 (3.6)	0 (0)
Muscle tremor	2 (1.8)	0 (0)
Signs of colitis	2 (1.8)	0 (0)
Hypothermia*	1 (0.9)	13 (11.5)
Vomiting	1 (0.9	6 (5.3)
Involuntary defecation	1 (0.9)	0 (0)
Nausea	1 (0.9)	0 (0)
Tachycardia, transient	1 (0.9)	0 (0)
Prolonged sedation	0 (0)	3 (2.7)
Urinary incontinence	0 (0)	2 (1.8)
Retching	0 (0)	1 (0.9)
Apnea	0 (0)	1 (0.9)
Bradycardia	0 (0)	1 (0.9)
Hyperthermia	0 (0)	1 (0.9)

*Hypothermia that necessitated use of an external heat source

Field Study Safety
Decreased body temperature occurred within 30 minutes after administration for some dogs in both treatment groups and lasted up to 2 hours in the Zenalpha group and 2-6 hours in the control group. There were 57/110 dogs (51.8%) in the Zenalpha group and 77/113 dogs (68.1%) in the control group that had a body temperature ≤99 °F. The respiratory rates decreased in both groups within 5 minutes post dose compared to baseline. The group mean respiratory rate in the Zenalpha group decreased earlier and recovered faster than the control group. Thirty-nine dogs out of 110 (35.4%) in the Zenalpha group and 33/113 dogs (29.2%) in the control group had respiratory rates < 10 breaths per minute (bpm) during the study. The group mean respiratory rate in the Zenalpha group was lowest at 30 minutes post-treatment (14 bpm) and in the control group was lowest at 90 minutes post-treatment (15.5 bpm). Mucous membrane color and capillary refill time were normal for all dogs at all timepoints during the study.

CONTACT INFORMATION:
To report suspected adverse reactions, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), call Dechra at (866) 933-2472. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY:
Medetomidine is a potent non-narcotic alpha$_2$-adrenoceptor agonist which produces sedation and analgesia. These effects are dose dependent in depth and duration. Medetomidine is a racemic mixture containing the active enantiomer dexmedetomidine. Within the central nervous system, sympathetic neurotransmission is inhibited and the level of consciousness decreases. Respiratory rate and body temperature can also decrease. In the peripheral vasculature, medetomidine stimulates alpha$_2$-adrenoceptors within vascular smooth muscle which induces vasoconstriction and hypertension which consequently decreases the heart rate and cardiac output. Dexmedetomidine also induces a number of other alpha$_2$-adrenoceptor mediated effects, which include piloerection, depression of motor and secretory functions of the gastrointestinal tract, diuresis and hyperglycemia.

Vatinoxan is a peripherally selective alpha$_2$-adrenoceptor antagonist which lacks activity in the central nervous system. By limiting its effects to peripheral organ systems, vatinoxan will prevent or attenuate the cardiovascular and other effects of dexmedetomidine outside the central nervous system when administered simultaneously with the alpha$_2$-adrenoceptor agonist. The central effects of dexmedetomidine remain unaltered, although vatinoxan will reduce the duration of sedation and analgesia induced by dexmedetomidine, predominantly by increasing the clearance of the latter via improving the cardiovascular function.

No pharmacokinetic assessment was performed on Zenalpha [medetomidine (1 mg/m^2) + vatinoxan (20 mg/m^2)]. However, after IM administration of a pilot formulation of medetomidine (1 mg/m^2) + vatinoxan (30 mg/m^2), both medetomidine and vatinoxan were rapidly and highly absorbed from the injection site. Maximal plasma concentration was reached at 12.6 ± 4.7 (mean ± standard deviation) minutes and 17.5 ± 7.4 minutes for dexmedetomidine (the active enantiomer of medetomidine) and vatinoxan, respectively. Vatinoxan increased the volume of distribution and the clearance of dexmedetomidine. Thus, the clearance of dexmedetomidine was increased two-fold when given in combination with vatinoxan. The same phenomena were also observed with intravenous administration.

Medetomidine plasma protein binding is high (85-90%). Medetomidine is mainly oxidized in the liver, a smaller amount undergoes methylation in the kidneys, and excretion is mainly via urine. Vatinoxan plasma protein binding is approximately 70%. Low levels are detectable in the central nervous system. Only a small amount (<5%) of vatinoxan dose has been found to be excreted via the urine.

EFFECTIVENESS:
A prospective, randomized, masked, multi-center study was conducted at six veterinary clinics to evaluate the effectiveness of Zenalpha to provide sedation and analgesia for non-painful or mildly painful, non-invasive procedures and examinations in client-owned dogs. Effectiveness was evaluated in 208 of the 223 enrolled dogs (109 in the Zenalpha group and 99 in the control group). Dogs ranged in age from 5 months to 14.5 years, weighed 5.1 to 154 lbs (2.3-70 kg) and represented purebreds and breed mixes. Dogs received one IM injection of Zenalpha at 1 mg/m^2 medetomidine and 20 mg/m^2 vatinoxan, or dexmedetomidine at 0.5 mg/m^2 (control group) to produce sedation prior to conduct of the examination or procedure. Procedures included: radiographic examination or diagnostic imaging, ear examination and treatment, eye examination and treatment, anal sac treatment, dermatological examination and procedures, dental examination, dental biopsy, dental minor extraction, fine needle aspiration/superficial biopsy, minor surgery to remove dermal masses, drain seroma or abscess, nail trimming, coat grooming, venous blood draw and intravenous catheter placement. Many dogs underwent more than one procedure while sedated.

Effectiveness of Zenalpha was based on: 1) the ability to complete the planned examination or procedure while the dog was sedated, and 2) demonstration of less severe cardiovascular adverse effects (determined by heart rate) compared to the control group. Respiratory rate, body temperature, analgesia, and adverse reactions were evaluated as secondary variables for the safety assessment (see Adverse Reactions). Dogs were evaluated at 5, 15, 30, 60, and 90 minutes and 2, 3, 4, 5 and 6 hours post-treatment. The success rate for ability to complete the procedure was 94.5% (103/109) in the Zenalpha group and 90.9% (90/99) in the control group. The Zenalpha group mean heart rate remained within the normal range (60-140 bpm), while the control group mean heart rate was below normal from 5-180 minutes post-treatment. The mean heart rate in the Zenalpha group was lowest at 15 minutes (64 bpm) and the mean heart rate in the control group was lowest at 90 minutes (45 bpm). There were 9 dogs (8.3%) in the Zenalpha group and 54 dogs (52.4%) in the control group that had heart rates <40 beats per minute (bpm) during sedation. Zenalpha met the criteria for success because it was not inferior to the control product for sedation and completion of the procedure and provided a decrease in the occurrence of bradycardia.

Dogs in the Zenalpha group typically had a shorter time to onset of sedation and shorter duration of sedation compared to the control group. The mean time to onset of sedation was 14 minutes in the Zenalpha group and 18 minutes in the control group. The mean duration of sedation in the Zenalpha group was 38 minutes (maximum of 90 min.) and in the control group was 90 minutes (maximum 5 hrs. 28 min.). The analgesic effects in the Zenalpha and the control groups were similar, and both waned with the loss of sedation.

The results of the field study demonstrated that Zenalpha is safe and effective, and provides sedation and analgesia needed to perform common non-painful or mildly painful veterinary examinations and procedures. Dogs treated with Zenalpha had a shorter time to onset of sedation, shorter duration of sedation (recovered quicker), and less cardiovascular and respiratory depression and adverse reactions compared to dogs in the control group.

ANIMAL SAFETY:
In a 4-day laboratory study using final market formulation, 32 healthy Beagle dogs (4 dogs/sex/group) aged 4.5 - 6.5 months were administered saline control, 1/20 medetomidine/vatinoxan, 3/60 medetomidine/vatinoxan, or 5/100 medetomidine/vatinoxan mg/m^2 Body Surface Area (BSA) by intravenous injection. These Zenalpha doses correspond to 1, 3, or 5X the recommended intramuscular dose. The administration of Zenalpha resulted in sedation, hypotension, hypothermia, and initially sinus bradycardia followed later by sinus tachycardia as the dogs recovered from sedation. Generally, dogs were provided supplemental heat support starting at 1 or 2 hours post-dose and continuing through 4 hours post-dose. Dogs recovered from sedation within 4 hours for the 1X group and 4-8 hours for the 3 and 5X groups. Physiologic variables returned to baseline within 8 hours post-dose in all dose groups. Bloodwork was evaluated 3-4 hours post-dose. Two dogs in the 5X group had decreased blood glucose on post-dose bloodwork. One dog in the 1X group and one dog in the 3X group had decreased potassium on post-dose bloodwork. Clinical observations included mucoid, soft, or watery feces and observations of salivation, trembling, tremors, vocalization, defecation or vomiting after dosing, injected sclera, struggling after dosing, and skin cool to touch. There were no Zenalpha-related effects on moribundity, body weight, ophthalmological examinations, mucous membrane color, capillary refill time, gross pathology observations, organ weights, or histopathological findings.

STORAGE INFORMATION:
Store below 77°F (25°C).
In use shelf life: 3 months at 77°F (25°C).
Protect from freezing and store in outer carton to protect from light.

HOW SUPPLIED:
Zenalpha is supplied in 10 mL multi-dose glass vials. Each mL contains 0.5 mg medetomidine hydrochloride and 10 mg vatinoxan hydrochloride.

NDC 17033-090-05

Approved by FDA under NADA # 141-551

Manufactured for:
Dechra Veterinary Products
7015 College Boulevard, Suite 525
Overland Park, KS 66211 USA

Manufactured in Sweden.

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