A review of the physiological effects of α_2-agonists related to the clinical use of medetomidine in small animal practice

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Abstract — Medetomidine is a relatively new sedative analgesic drug that is approved for use in dogs in Canada. It is the most potent α_2-adrenoreceptor available for clinical use in veterinary medicine and stimulates receptors centrally to produce dose-dependent sedation and analgesia. Significant dose sparing properties occur when medetomidine is combined with other anesthetic agents correlating with the high affinity of this drug to the α_2-adrenoreceptor. Hypoventilation occurs with medetomidine sedation in dogs; however, respiratory depression becomes most significant when given in combination with other sedative or injectable agents. The typical negative cardiovascular effects produced with other α_2-agonists (bradycardia, bradyarrhythmias, a reduction in cardiac output, hypertension ± hypotension) are also produced with medetomidine, warranting precautions when it is used and necessitating appropriate patient selection (young, middle-aged healthy animals). While hypotension may occur, sedative doses of medetomidine typically raise the blood pressure, due to the effect on peripheral α_2-adrenoreceptors. Anticholinergic premedication has been recommended with α_2-agonists to prevent bradyarrhythmias and, potentially, the reduction in cardiac output produced by these agents; however, current research does not demonstrate a clear improvement in cardiovascular function. Negatively, the anticholinergic induced increase in heart rate potentiates the α_2-agonist mediated hypertension and may increase myocardial oxygen tension, demand, and workload. Overall, reversal with the specific antagonist atipamezole is recommended when significant cardiorespiratory complications occur. Other physiological effects of medetomidine sedation include; vomiting, increased urine volumes, changes to endocrine function and uterine activity, decreased intestinal motility, decreased intraocular pressure and potentially hypothermia, muscle twitching, and cyanosis. Decreased doses of medetomidine, compared with the recommended label dose, should be considered in combination with other sedatives to enhance sedation and analgesia and lower the duration and potential severity of the negative cardiovascular side effects. The literature was searched in Pubmed, Medline, Agricola, CAB direct, and Biological Sciences.

Résumé — Étude des effets physiologiques des agonistes α_2 reliés à l'administration de la médétomidine à des petits animaux. La médétomidine est un produit analgésique et sédatif relativement récent, qui a été homologué au Canada pour être administré aux chiens. Il est actuellement l'agent adrénorécepteur α_2 le plus puissant pour l'utilisation clinique en médecine vétérinaire; il stimule les récepteurs centralement pour induire une analgésie et une sédation proportionnelles à la dose. La dose peut être considérablement diminuée lorsqu'on combine la médétomidine avec d'autres agents analgésiques, en raison de la grande affinité de ce produit pour les adrénorécepteurs α_2. La médétomidine produit de l'hypoventilation chez les chiens; par contre cette dépression respiratoire est plus importante lorsque le produit est administré en combinaison avec d'autres agents sédatifs ou injectables. Les effets secondaires cardiovasculaires causés par d'autres agonistes α_2 (bradycardie, bradyarythmie, diminution du débit cardiaque, hypertension ± hypotension) sont aussi produits par la médétomidine; il faut donc prendre des précautions lors de son utilisation et choisir les patients avec discernement (animaux jeunes ou d'âge moyen et en bonne santé). Bien qu'elles puissent causer de l'hypotension, une dose de médétomidine induisant une sédation fait généralement augmenter la pression sanguine, à cause des effets sur les adrénorécepteurs α_2 périphériques. L'administration préalable d'un anticholinergique est recommandée lors de l'utilisation des agonistes α_2 afin de prévenir la bradyarythmie et même la réduction du débit cardiaque que produisent ces agents; toutefois, la recherche actuelle ne montre pas d'amélioration importante de la fonction cardiovasculaire. Par ailleurs, l'augmentation du rythme cardiaque produite par l'anticholinergique potentialise

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l'hypertension causée par l'agoniste α_2, et elle peut provoquer une augmentation de la tension et de la demande en oxygène du myocarde, et de l'effort qu'il doit fournir. En résumé, l'administration de l'antagoniste spécifique atipamézole est recommandée lorsque des complications cardiorespiratoires graves surviennent. L'administration de la médétomidine comme sédatif peut causer d'autres effets secondaires, notamment des vomissements, une augmentation du volumes urinaire, un changement des fonctions endocrines et de l'activité utérine, une diminution de la motilité intestinale, une diminution de la pression intraoculaire, voire de l'hypothermie potentielle, des spasmes musculaires et de la cyanose. Une dose plus faible que celle recommandée par le fabricant devrait être administrée lorsque ce produit est utilisé en combinaison avec d'autres sédatifs afin d'augmenter la sédation et l'analgésie et de diminuer la durée et la gravité des effets secondaires cardiovasculaires éventuels. La documentation consultée provient de Pubmed, Medline, Agricola, CAB direct et Biological Sciences.

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Introduction

Medetomidine is a potent and highly specific α_2-adrenoreceptor agonist that has been used extensively in Europe and is registered in 34 countries world-wide. It is licensed for IM and IV use only in dogs in Canada and the United States, but in other countries, such as the United Kingdom and Finland, it is approved for use in both dogs and cats. Medetomidine is a lipophillic compound that is rapidly and completely absorbed after IM injection. The absorption half-life is approximately 7 min with peak serum levels at 30 min in the dog (1). The drug is not licensed for SC use, due to potentially less reliable and incomplete sedation compared with IM administration (2). It is supplied as a 0.1% or 1 mg/mL (1000 μg/mL) solution and is marketed as a racemic mixture of 2 stereoisomers, dextro-medetomidine and levo-medetomidine. The dextro-isomer, dexmedetomidine, is the active isomer of the medetomidine formulation and when administered at half the dose induces similar effects to medetomidine (3,4). Dexmedetomidine is currently not marketed for veterinary medicine; however, research using this isomer has been performed in dogs and cats and this information is included in this review. The levo-isomer, levomedetomdine, lacks pharmacological activity and only shows mild sedative and analgesic properties at high doses (3).

The beneficial effects of medetomidine are the same as those of other α_2-agonists and include reliable sedation, analgesia, muscle relaxation, and anxiolysis, as well as a decrease in the anesthetic requirements of injectable and inhalant agents (anesthetic sparing). It is not a controlled substance and, therefore, does not require extensive record keeping. These qualities make medetomidine a viable option in small animal anesthesia. Unfortunately, the negative cardiovascular effects of earlier α_2-agonists (xylazine), including bradycardia and associated arrhythmias, hypertension or hypotension, and reduced cardiac output, are still observed with medetomidine and cause concern among clinicians with respect to their use as premedication or sedative agents.

When xylazine was introduced on the veterinary market, its potency was not always respected and it was used indiscriminately on all types of patients at high doses, without consideration always being given to the dose sparing benefits of these agents. This was compounded by the fact that there were no commercially available reversal agents at this time. It is likely that the manner in which xylazine was used in combination with the negative cardiovascular effects resulted in the increase in mortality rate in healthy dogs demonstrated with xylazine premedication compared with other preanesthetic regimes in the mortality studies to date (5,6). Comparable clinical data are not yet available for medetomidine.

With this history in mind, practitioners need to 1) review the general physiologic effects of α_2-agonists; 2) recognize the significant dose sparing effect and added respiratory depression that occurs when these drugs are used in combination with other sedatives, injectable anesthetics, inhalant anesthetics, or both; and 3) consider using clinically lowered doses of these agents. The purpose of this article is to provide the reader with an overview of the main physiologic effects of α_2-agonists and to provide a summary of the current scientific and clinical data on the use of medetomidine in small animals. The literature cited was highlighted from searches of Pubmed, Medline, Agricola, CAB-direct, and Biological Sciences encompassing the relevant physiologic effects of α_2-agonists, specifically medetomidine, in dogs and cats.

Alpha$_2$ adrenoreceptors

The α_2-adrenoreceptor is a distinct subclassification of α-adrenergic receptors, which are located in the central nervous system (CNS) and virtually every peripheral tissue (7). Alpha$_2$-adrenoreceptors are comprised of numerous subtypes, α_{2A}, α_{2B}, α_{2C}, and α_{2D}, based on classical pharmacologic and molecular biologic studies (7–9), and these subtypes are distributed throughout the CNS (9,10). The diversity in α_2-adrenoreceptor subtype, density, and location in animals and humans has led to considerable differences in drug doses and overall effects of α_2-agonists in the various species. The receptor subtypes of general clinical importance include the α_{2A} subtype, which regulates the stage of awareness, arousal, and vigilance in the brainstem, and the α_{2B} subtype, which regulates the peripheral vasoconstrictive effects (7). Species differences exist, based on the proportion of these subtypes centrally at the level of the brainstem. For example, α_{2A} subtypes predominate in canine and rat brainstems (11), while the α_{2D} subtype appears to predominate in the sheep brainstem (12). It is interesting to speculate that ruminants as a group may primarily harbor the α_{2D} adrenergic receptor homologue

of the α_{2A} adrenergic receptor within the brainstem, since compared with other species, they have greater sensitivity to the sedative effects of α_2-agonists.

Clinically, the degree of sedation and analgesia produced by an α_2-agonist is related not only to the density, location, and type of α_2-adrenoreceptors within the animal, but also to the individual selectivity and affinity of the drug molecule between the α_1 and α_2 receptor binding sites. Most currently available α_2-agonists can activate the α_1-adrenoreceptors; therefore, these receptors play some part in the effect of these agents, especially nonspecific agents such as xylazine. Activation of α_1-adrenoreceptors induces arousal, restlessness, increased locomotor activity, and increased vigilance (13). These effects may be noted when high doses (4 and 8 mg/kg BW) of xylazine are used (14). Studies have demonstrated that central α_1-adrenoreceptor stimulation antagonizes the hypnotic response to even potent α_2-agonists, such as dexmedetomidine (15), and that the α_1-adrenoreceptor effects will predominate with increased or toxic doses of α_2-agonists (16,17).

At clinical doses, the more selective a drug is to the α_2-adrenoreceptor, the more potent it is, so that a lowered dose, and hence a smaller injection volume, is required to achieve a similar degree of sedation. The following order of α_2/α_1 selectivity has been reported: medetomidine (1620:1), detomidine (260:1), clonidine (220:1), and xylazine (160:1) (18,19). The selectivity of romifidine has not been documented, although, clinically, it appears to be between xylazine and detomidine.

Physiological effects of α_2-agonists

Sedative effects

The interest in the use of α_2-agonists in veterinary anesthesia is related to the ability of these drugs to produce reliable sedation and anxiolysis. These effects are mediated by receptors located primarily in locus coeruleus neurons on the pons and lower brainstem (20–23). Alpha$_2$-agonists bind with and intrinsically change the membranes of the α_2-adrenoreceptors, preventing further release of the neurotransmitter norepinephrine. Centrally, norepinephrine is necessary for arousal. If the release of norepinephrine is blocked, the net result is sedation.

Failure to achieve optimum sedation with α_2-agonists may be due to preexisting stress, fear, excitement, or pain, as all of these conditions can increase endogenous catecholamine levels that interfere with α_2-agonist-induced reductions in excitatory neurotransmitter release. Extremely apprehensive patients may prove refractory to the sedative actions of α_2-agonists. Sedation is consistently achieved when α_2-agonists are given to patients in calm and quiet surroundings with minimal environmental stimuli. Dogs or cats that appear sedated may suddenly become aroused and aggressive, if disturbed, and many demonstrate an increased sensitivity to sound and initial tactile stimulation (24).

Cardiovascular effects

Alpha$_2$-adrenoreceptor agonists, through stimulation of central and peripheral adrenoreceptors, significantly affect cardiovascular function, which becomes most significant in sick, unstable, or cardiovascular compromised patients (25,26). The main negative cardiovascular effects of all α_2-agonists include bradycardia and associated bradyarrhythmias (1st and 2nd degree atrioventricular heart block), a dramatic reduction in cardiac output (CO) by up to 50% (L blood/min), and an increase in systemic vascular resistance (SVR) (27–29).

It is important to realize that there are actually 2 main causes of the α_2-agonist-induced bradycardia: diminished sympathetic tone and increased SVR. Alpha$_2$-agonists reduce norepinephrine outflow within the CNS, thus dampening central sympathetic tone and beneficially resulting in sedation, but the reduced sympathetic tone also promotes a reduction in heart rate (HR). The action of the α_2-agonist at the peripheral α_2-adrenoreceptors accounts for the dramatic increase in SVR, which will be recognized clinically as an increase in arterial blood pressure. When medetomidine is administered alone at a dose of 40 μg/kg BW, IV to healthy beagle dogs, there is a dramatic increase in mean arterial blood pressure (MAP) (average of 175 mmHg within 3 min) (29). This hypertension induces a reflex baroreceptor-mediated physiologic bradycardia, associated bradyarrhythmias, and dramatic reduction in CO, which is perpetuated by the central effects of sedation and reduced sympathetic tone. Various research articles have demonstrated that the drop in CO is not due to a direct negative action of the α_2-agonist on myocardial contractility, but is secondary to the increased SVR and reduced HR (30–32).

Over time, the peripheral effects of the α_2-agonist will subside, and the blood pressure will decrease towards normal (33). The extent and duration at which an α_2-agonist will increase SVR depends on several factors: 1) Selectivity of the drug at the α_2-adrenoreceptor; 2) dose (high or low), and 3) route of drug administration, IV or IM.

Xylazine has been noted to increase systemic blood pressure, but this effect is generally not as profound or as long standing as that of medetomidine (34). In fact, an early report on the effects of xylazine warns of a potential hypotension (35). In small animals sedated with medetomidine alone, clinically significant hypotension (MAP $<$ 60–80 mmHg) is unlikely to result due to the increased selectivity of this drug at the α_2-adrenoreceptor. Hypotension is more likely to result when α_2-agonists are administered with other sedatives or anesthetics. Blood pressure in dogs (29,36,37) and cats (38) sedated with medetomidine alone is elevated in a dose dependent manner initially, but it will decrease over time to more normal levels. Analysis of the results of various studies on the use of medetomidine in dogs did not reveal clinically significant hypotension during the study periods, but a general trend of decreasing blood pressure toward baseline or normal levels (29,33,34,36,37,39,40). For example, in dogs sedated with medetomidine (10 μg/kg BW, IV), initial values of MAP were on average 140 to 160 mmHg, which decreased to an average of 90 to 110 mmHg within 1 h (29).

Cats do not appear to have the same degree of hypertension associated with the sole administration of dexmedetomidine (41) or medetomidine (42). Lamont et al (42) concluded that the cats in their study were potentially stressed during baseline measurements, which

caused increased concentrations of circulating catecholamines and a relatively high baseline MAP (139 mmHg) and prevented substantial increases in pressure values from being detected when the cats were sedated with medetomidine (42). Stress and heightened circulating catecholamine levels could also be a contributing factor in the effects of dexmedetomidine reported by Selmi et al (41); however, these authors suggested that the different pressor response might be associated with a predominance of central α_2-adrenergic effects over peripheral vascular effects in the cat. When cats were anesthetized prior to medetomidine administration, an increase in systemic blood pressure occurred, as in other species (38,43). For example, in cats anesthetized with isoflurane, the MAP increased from a baseline of 77 mmHg to 132 mmHg with medetomidine (10 μg/kg BW, IM), which suggests that a pressor response occurs in cats as well (38).

Increases in arterial blood pressure are typically dose related with the administration of medetomidine, the higher the dose the more profound the increase. Lower doses of α_2-agonists may be associated with more predominant CNS effects, whereas higher doses probably cause a more pronounced stimulation of peripheral adrenoreceptors and vasoconstriction (29). Not only is the dose important, the route of administration also plays a role on the extent of increased systemic vascular resistance. The initial hypertension is greater when the α_2-agonist is administered, IV, than when it is administered, IM (34). Vainio and Palmu (34) demonstrated a 26% increase in MAP after medetomidine or xylazine was administered, IV, compared with an 18% increase when the same doses were administered, IM. The differences in the initial blood pressure response with different routes of drug administration are likely related to variations in the speed of uptake and absorption of the drug on the overall effect at the peripheral adrenoreceptors (34). Based on these findings, it is typically recommended that lowered doses of α_2-agonists be administered, IM, to avoid extremes of blood pressure.

Respiratory effects

Sedation with α_2-agonists results in a reduction in respiratory rate for varying periods. Respiratory depression occurs secondary to the CNS depression produced by α_2-adrenoreceptor stimulation; however, the degree of depression with α_2-agonists alone is less than that with other sedatives, even at sublethal doses (27). In dogs at doses between 20 and 60 μg/kg BW, medetomidine significantly depressed respiratory rate (2,34,44). In those studies in which arterial blood gas tensions were measured, an increased arterial carbon dioxide tension was observed; however, the reductions in arterial oxygen tensions were not significant when medetomidine was administered alone (36,39,45,46). These results are consistent with those in studies of romifidine administered at 40 and 120 μg/kg BW in dogs, when a decrease in respiratory rate without significant alterations in arterial blood gases was noted (47). In cats, dexmedetomidine alone did not reduce respiratory rate (41) and medetomidine alone did not alter arterial blood gas values significantly (42).

It is important to realize that the degree and significance of respiratory depression produced with any α_2-agonist will be increased when the agonist is given with other sedatives. Decreased respiratory rate, increased arterial carbon dioxide tension (48,49), hypoxemia and cyanosis (49–52) have been reported in dogs premedicated with medetomidine and induced with propofol. The respiratory rate was significantly decreased in dogs sedated with medetomidine (30 μg/kg BW, IM) and butorphanol (0.2 mg/kg BW, IM), compared with that in dogs sedated with medetomidine (30 μg/kg BW, IM) alone or medetomidine with ketamine (3 mg/kg BW, IM) (39). In this latter study, a respiratory acidosis and a significantly lowered arterial oxygen tension in the medetomidine/butorphanol group (as low 64 mmHg, 20 min after administration) and the medetomidine/ketamine group (as low as 61 mmHg, 5 min after administration) were observed with all drug combinations. Other studies with medetomidine and opioids in dogs also concluded that there is greater respiratory depression, acidosis, and potential hypoxemia when these drugs are administered together (45,53,54). Respiratory depression has also been reported in cats when dexmedetomidine-butorphanol or dexmedetomidine-ketamine (41) combinations and medetomidine-ketamine combinations were administered (55,56,57). Based on these reports, oxygen should be administered by face-mask or endotracheal intubation when α_2-agonists are used in combination with other sedatives or injectable anesthetics, respectively.

Cyanosis has been reported in up to 33% of dogs that have been sedated with medetomidine (2,24,54,58). Cyanosis is obvious when the unoxygenated hemoglobin concentration is $>$ 50 g/L of blood and can develop from 3 mechanisms (59). Clinically, cyanosis is generally considered to develop either when blood is insufficiently oxygenated in the lungs or when hemoglobin is unable to carry oxygen. The 3rd mechanism of cyanosis development involves the stagnation of blood within peripheral capillary beds, which results in increased oxygen extraction. In the above reports of cyanosis in association with the administration of medetomidine, the animals had no significant reductions in arterial oxygen content and arterial oxygen saturation remained above 95%; however, venous oxygen tensions and filling were low. Thus, the cyanosis observed with the administration of medetomidine is likely due to low blood flow through peripheral capillary beds and an actual venous desaturation; however, this theory has yet to be proven in the trials to date. Although cyanosis may be observed in small animals, more commonly, the mucous membranes are pale secondary to the peripheral α_2-mediated vasoconstriction.

Muscle relaxation

It has long been recognized that α_2-agonists provide muscle relaxation and analgesia (26). The muscle relaxant effect that accompanies sedation is due to inhibition at α_2-adrenoreceptors at the interneuron level of the spinal cord and is a beneficial property of the α_2-agonists in veterinary medicine (25). Interestingly, tizanide, a new α_2-agonist used in human medicine, has been found to be effective in relieving muscle spasticity resulting from

stroke, cerebral trauma, and multiple sclerosis, because of its profound muscle relaxant properties (60–62).

Analgesia

Alpha$_2$-agonists produce analgesia by stimulating receptors at various sites in the pain pathway within the brain and spinal cord (63). Radioligand studies have demonstrated high concentrations of α_2-adrenoreceptor binding sites in the dorsal horn of the spinal cord where nociceptive fibers synapse (64) and in the brainstem where modulation of nociceptive signals are likely to be started (65). Electrophysiological studies have indicated that pre- and postsynaptic inhibitory mechanisms are responsible for the antinociceptive action of α_2-adrenoreceptor agonists (66).

In the modulation of pain, there are interactions between opiate receptors and α_2-adrenoreceptors in the brain (33) and spinal cord (67,68). Alpha$_2$ and opioid receptors are found in similar regions of the brain and even on some of the same neurons. These receptors share common molecular machinery beyond that of the receptor. Binding of either α_2-agonists or μ-opioid agonists to their receptors results in activation of the same signal transduction systems (membrane associated G proteins), which induces a chain of events that open potassium channels in the neuronal membrane. Activation of potassium channels in the postsynaptic neuron leads to hyperpolarization of the cell, which ultimately makes the cell unresponsive to excitatory input and effectively severs the pain pathway. Consequently, the α_2-agonists and μ-opioid agonists produce analgesia by similar mechanisms.

Experimental and clinical evidence indicates that analgesia is not present throughout the entire period of sedation with α_2-agonists and that these agents alone are not suitable for painful or major surgical procedures. The analgesic effects of these agents typically only last for half the duration of the sedation. For example, medetomidine administered at 20 to 40 μg/kg BW will induce sedation for 60 to 90 min, while its analgesic effects may last for only 30 to 45 min (25), and if painful manipulations are continued, the period of sedation will be shortened and recovery will be hastened. In general, α_2-agonists should be combined with local anesthetics or other anesthetic agents for surgical procedures. Current research on the use microdoses of α_2-agonists for acute and chronic pain have demonstrated their usefulness both systemically and epidurally (69–72); however, the sedative and cardiovascular effects that accompany analgesia with α_2-agonists may be undesirable.

Other effects

Hypothermia

Temperatures may decrease in animals sedated with α_2-agonists. In general, the reduction in temperature with α_2-agonists can be attributed to CNS depression, in combination with a reduction in muscular activity (73,74). However, in dogs, only slight reductions in rectal temperature were observed with medetomidine (29,46,74,75) or romifidine (76), while no reductions were noted with romifidine sedation (47,77,78,79,80). Alpha$_2$-agonists may allow for better maintenance of body temperature due to the peripheral vasoconstriction and central redistribution of blood, with a consequent reduction in cutaneous heat losses, in contrast to the consistent reductions in body temperature reported with the use of other anesthetic agents that induce vasodilation. However, body temperature should still be monitored in small animals and appropriate attempts should be made to conserve body heat and prevent dramatic reductions in temperature.

Muscle twitching

Muscle twitching following sedation with medetomidine has been described in some dogs (2,24,54,58,81–83) and cats (55,57,58). Similar twitching has also been observed in dogs sedated with xylazine (84) and romifidine (78,85). It has been speculated that because the muscle twitching occurs more frequently in animals in a noisy environment, hypersensitivity to noise may be a possible explanation for it (2). However, muscle twitching was not noted in studies in which the α_2-agonist was administered, IM (76), compared with other studies in which it was administered, IV (85). Therefore, the occurrence of twitching may depend not only on the environment but also on the drug, the route of administration, and the absorption rate.

Endocrine

Various studies have shown that α_2-agonists reduce the perioperative levels of stress-related hormones and thus attenuate the stress response of surgery in dogs (14,86–88). In human anesthesia and surgery, the stress response is an important factor contributing to patient morbidity; therefore, preanesthetics include an α_2-agonist to minimize this response (89). The importance of the stress response that is associated with surgery in veterinary medicine is still unknown; however, there is increasing interest in using medetomidine as a preanaesthetic to promote balanced anesthesia and minimize the overall stress response (86,88).

Alpha$_2$-agonists, typically xylazine, have been reported to induce an increase in serum glucose by suppressing insulin release, stimulating glucagon release, or both, in β and α cells of the pancreas, respectively (90,91). However, medetomidine given at doses of 10 and 20 μg/kg BW, IV, decreased insulin values significantly but was not found to alter plasma glucose concentrations in normal beagles (92). Differences in plasma glucose concentrations are likely associated with the greater specificity of medetomidine, compared with that of xylazine, at the α_2-adrenoreceptors. The hyperglycemia associated with xylazine has been attributed to the actions at both the α_2- and α_1-adrenoreceptors. In cattle, the xylazine induced hyperglycemia is reversed with the α_1-adrenoreceptor antagonist prazosin (93). Despite this, the use of medetomidine in animals with diabetes mellitus cannot be recommended until more information is available.

It is well recognized that animals recovering from α_2-agonist sedation typically have large volumes of urine with low specific gravity (2,24,94). Administration of medetomidine at dosages of 10 and 20 μg/kg BW, IV, induced a diuretic effect that lasted for up to 4 h (95).

Xylazine administration has also been associated with increased urine production in several species (96–98). This diuretic effect negates the use of these agents in animals with a urinary tract obstruction.

Reasons for the diuresis involve the actions of α_2-agonists on antidiuretic hormone (ADH) and the renin-angiotensin system. Central stimulation of α_2-adrenoreceptors in the hypothalamus by α_2-agonists was reported to decrease the secretion, production, or both, of ADH from the pituitary gland in dogs and rats (99,100); however, other authors have postulated that ADH is indirectly decreased due to the circulatory changes induced with α_2-agonist sedation (101). Alpha$_2$-agonists have also been shown to have a peripheral renal effect due to their antagonism of the renal tubular effects of ADH (102,103) and their potentiation of urinary sodium output (104,105).

Sedation with α_2-agonists can also impact the renin-angiotensin system directly or indirectly. Experiments in vitro have demonstrated a clear decrease in renin production directly via specific renal α_2-adrenoreceptors (106); however, the renin-angiotensin system may also be affected indirectly by α_2-agonist-induced hypertension (107). Alpha$_2$-agonists also potentiate the release of growth hormone (108), although it is unlikely that the clinical implications of this are serious.

Arrhythmogenecity

The administration of medetomidine to dogs frequently causes a reduction in heart rate by as much as 30% to 50% (25). Vagal-induced bradyarrhythmias, 1st and 2nd degree atrioventricular heart block, are also commonly reported in the dog (109). Typically, these arrhythmias are not life threatening and are attributed to a baroreceptor mediated reflex to the peripheral vasoconstriction and a diminished sympathetic outflow, as described above. Rarely, and more consequentially, 3rd degree atrioventricular heart block and sinus arrest may occur with α_2-agonist sedation (110). In cats, bradycardia is also typically associated with medetomidine sedation, with reductions in heart rate from 30% to 40% (16,42,111,112). However, only sinus bradycardia was reported when rhythm was recorded electrocardiographically (111).

Despite its association with these common bradyarrhythmias, medetomidine is not, by definition, arrhythmogenic. Arrhythmogenecity of anesthetics refers to the ability of the drug to induce myocardial sensitivity to epinephrine and promote ventricular arrhythmias. Scientifically, this is defined as the arrhythmogenic dose of epinephrine (ADE). A lowering of the ADE, or dose of epinephrine required to produce an arrhythmia with an anesthetic agent, increases the arrhythmogenecity of the agent. Various studies have looked at alterations in the arrhythmogenicity in α_2-agonist sedated animals and have found that the occurence of arrhythmogenecity is dependent on the selectivity of the α_2-agonist, its dose, and the route of administration (113). Typically the less selective α_2-agonists are more arrhythmogenic and the more selective α_2-agonists actually prevent epinephrine induced arrhythmias. It is likely that arrhythmogenecity is mediated by α_1-adrenoreceptors and that stimulation of central α_2-adrenoreceptors by the more selective α_2-agonists reduces arrhythmogenicity by decreasing sympathetic tone and enhancing parasympathetic tone. For example, administration of xylazine decreases the ADE required to induce ventricular arrhythmias in halothane- (114,115) and isoflurane- (116) anesthetized dogs; however, the more selective α_2-agonists, detomidine, medetomidine, and dexmedetomidine, do not decrease the ADE: Intramuscular administration of medetomidine does not alter the ADE in dogs anesthetized with halothane (117) or isoflurane (118), and dexmedetomidine may even increase the ADE dose dependently in halothane-anesthetized dogs (119).

Uterine activity

Drugs stimulating α-adrenoreceptors increase the contractility of the pregnant (120) and nonpregnant (120,121) uterus. Xylazine, like oxytocin, causes contraction of the bovine uterus (122); therefore, anesthesia textbooks caution the use of xylazine in heavily pregnant cows due to anecdotal reports of premature labor and abortions (84,123). However, the administration of small doses of detomidine in pregnant cows (124) and clinical doses of medetomidine in pregnant dogs (120) leads to a decrease in myometrial contractility. No abortions were observed in either study, but in the canine study, an increase in the activity of the myometrium was noted in all cases during the postparturient period. The effect of drugs that stimulate the α-adrenoreceptors depends to a high degree on the level of steroid hormones: An increased level of estrogen increases the sensitivity of the α-adrenoreceptors, while a high level of progesterone during pregnancy stimulates the sensitivity of β-adrenoreceptors and actually decreases the contractility of the uterus (120). No literature was found that related the effects of α_2-agonists on the feline uterus. Overall, based on the literature reviewed, the use of medetomidine does not appear to promote abortions in pregnant dogs; however, the drug company does not recommend medetomidine for use in breeding or pregnant dogs.

Vomiting

In small animals, α_2-agonists typically induce vomiting by stimulating the chemoreceptor trigger zone, which is in close proximity to the locus coeruleus in the brain (125). Xylazine induces vomiting during early sedation in as many as 50% of dogs and 90% of cats (84). With medetomidine sedation, vomiting was observed in 8% to 20% of dogs (2,24,46,58,81–83,126) and up to 90% of cats (58,83).

Gastrointestinal motility

The adrenergic regulation of gastrointestinal secretions and motility seems to be mainly dependent on the activation or inhibition of α_2-adrenoreceptors located both presynaptically and postsynaptically. In general, α_2-agonists decrease gastric acid secretion (127,128), prolong intestinal transit time (129,130), and inhibit reticuloruminal contractions and colonic motility in sheep and cattle (131) and in horses (132). The gastrointestinal suppression is affected by dose and specificity of the α_2-agonist. Medetomidine was demonstrated to inhibit the electrical activity of the small intestine and dramatically inhibit the motility of the colon in dogs

(133). These effects were completely antagonized by the α_2-adrenergic antagonist atipamezole, confirming that the effect on gastrointestinal motility is mediated through α_2-adrenoreceptors.

Intraocular pressure

Mydriasis is reported to occur after α_2-agonist administration in animals. This effect is postulated to occur from central inhibition of parasympathetic tone to the iris, a direct sympathetic stimulation of the α_2-adrenoreceptors located in the iris, CNS, or both (134,135). Topical administration of medetomidine in the eye of rabbits and cats readily induces mydriasis and decreases intraocular pressure by suppressing sympathetic neuronal function and decreasing aqueous flow (135). However, the IV administration of medetomidine to dogs induced miosis and did not lower intraocular pressure (136). Despite these conflicting results, the detrimental effects of vomiting and lowered head posture on the intraocular pressure induced with medetomidine sedation would contraindicate the use of α_2-agonists in small animal patients with ocular problems in which an increase in intraocular pressure would be detrimental.

Intracranial pressure

A primary consideration in the anesthetic management of animals with intracranial lesions is the prevention of increased intracranial pressures (ICP). Studies have indicated that α_2-agonists lower cerebral blood flow via α_2-adrenoreceptor-mediated vasoconstriction, and hence ICP, in mechanically ventilated dogs anesthetized with isoflurane (137,138). The α_2-agonists may possess a role in anesthetic supplementation in cases with increased ICP; however, consideration must be given to the detrimental effects of vomiting and hyperglycemia induced by them.

Anesthetic sparing properties

One of the primary reasons for using α_2-agonists in veterinary medicine is their potent anesthetic sparing effect of injectable and inhalant anesthetics. The anesthetic sparing effect roughly correlates with the affinity of the drugs for the α_2-adrenoreceptors (7). That is, the more specific the α_2-agonist, the greater the anesthetic sparing effect. For example, in dogs, premedication with either romifidine or medetomidine, followed by induction with propofol, leads to marked synergism between the drugs (44,48,80). Romifidine at 20 μg/kg BW reduced the induction dose of propofol by 60% (80). Medetomidine has been found to decrease the dose requirements of propofol for induction and maintenance up to 75%, depending on the dose administered for premedication (44,48–52). Dose reductions of propofol to 1 mg/kg BW are recommended with medetomidine at premedication doses of 20 to 40 μg/kg, BW (139). Similarly, both medetomidine (81) and romifidine (77) markedly reduced the thiopentone induction dose in dogs by up to 75%.

Alpha$_2$-agonists also dramatically reduce the mean alveolar concentration (MAC) of the inhalant anesthetics. In dogs, clonidine (20 μg/kg BW, IV) reduced the MAC of halothane by 48% (140). Similarly, xylazine (1.1 mg/kg BW, IV) reduced the MAC of halothane in dogs by 39% (141), while medetomidine (30 μg/kg BW, IV) reduced the MAC of isoflurane by 47.2% (142). Dexmedetomidine, the active isomer of medetomidine, at 10 μg/kg BW, IV produced a 90% reduction in the MAC of halothane in dogs (143). The mechanisms by which the α_2-agonists potentiate the anesthetic effects of inhalant anesthetics have not been fully clarified. Alpha$_2$-agonist drugs do not share a common receptor mechanism with inhalant anesthetics, as demonstrated by the inability of α_2-antagonists to reverse halothane anesthesia; however, a synergism likely exists with these agents as both increase potassium conductance and induce neuronal hyperpolarization in the brain (18).

Antagonism

An added benefit of the α_2-agonists in clinical practice is the reversibility of their effects with the α_2-antagonists. There are at least 4 α_2-antagonists available in veterinary practice: yohimbine, tolazoline, atipamezole, and idazoxan. These α_2-antagonists exhibit individual selectivity and affinity for the α_2 and α_1 receptors, similar to the α_2-agonists. The α_2/α_1 reversal specificity of the antagonist drugs is as follows: atipamezole > idazoxan > yohimbine > tolazoline (7). If both the α_2-agonists and α_2-antagonist have a high receptor specificity and selectivity, reversal results in an animal not being different from untreated state. This competitive antagonism is especially important in reversing potentially threatening cardiovascular complications with routine doses, or in situations of inadvertent overdose.

Atipamezole, with the highest α_2-receptor selectivity (8500:1 in comparison with idazoxan) (18), is the preferred antagonist for reversal of medetomidine and may also be used to antagonize other α_2-agonists, such as xylazine or detomidine (144). Atipamezole (Antisedan, 5 mg/mL; Novartis Animal Health Canada, Mississauga, Ontario) is marketed with medetomidine. Other advantages of atipamezole compared with the less selective antagonists are the lack of activity at beta, histaminergic, serotonergic, dopaminergic, GABA-ergic, opioid, or benzodiazepine receptor sites (145). At a dose 4 to 6 times the dose of medetomidine, atipamezole administered, IM, will efficiently antagonize the sedative and behavioral effects of medetomidine within 3 to 7 min (24). The half-life of atipamezole is twice that of medetomidine; therefore, resedation is uncommon, although, occasional resedation has been reported in dogs and cats (81).

The use of these antagonists may also have adverse effects, like hypotension, tachycardia, excitement, and the removal of the α_2-agonist induced analgesia (146–148). Death has also been reported following rapid IV administration of yohimbine and tolazoline to xylazine-sedated sheep (148). Abrupt changes in cardiovascular function occur after IV administration; therefore, IM administration of atimpamezole is recommended to allow for a gradual awakening and to minimize the changes in blood pressure, HR, and CO (144). A transient hypotension may still occur even with IM administration of atimpamezole in medetomidine-sedated dogs (149). This may not be clinically significant in healthy stable animals;

however, clinicians should be aware of this side effect. In unsedated animals, inadvertent administration of atipamezole may cause minor excitatory effects and an increase in circulating plasma levels of norepinephrine (27). Atipamezole is not licensed for IV use, due to these potential complications; however, in emergency situations, IV administration is appropriate.

The use of anticholinergics with α_2-agonists

It is likely that all small animal patients will become bradycardic after sedation with an α_2-agonist, secondary to the baroreceptor reflex to hypertension and reduction in sympathetic tone. Anticholinergic premedication with α_2-agonists has been recommended to prevent bradyarrhythmias and, potentially, a reduction in cardiac output (150), and this recommendation has been widely adopted within most veterinary practices. However, conflicting opinions exist in various articles with respect to treating α_2-agonist mediated bradycardia and decreases in cardiac output with anticholinergics (25,26,29,34,144,151–154). Some authors have recommended reversal of the α_2-agonist as the safest remedy for bradycardia due to the potential detrimental cardiovascular effects of using anticholinergics with α_2-agonists (29,47,108).

Few authors have actually addressed the direct cardiovascular effects of using an anticholinergic with an α_2-agonist alone or in combination with opioids, or injectable or inhalant anesthetics. In the research involving anticholinergics and sedative doses of α_2-agonists, a clear improvement in cardiovascular function was not noted in either dogs (47,154) or cats (152). Overall, the anticholinergic-induced increase in HR potentiated the α_2-agonist mediated hypertension (34,37,47,151,152, 155–158), and it was speculated that it increased myocardial tension, oxygen demand, and workload (47,152,154,159).

Typically, preemptive administration of an anticholinergic prevents the reduction in HR and associated bradyarrhythmias associated with an α_2-agonist (37,47,155), but it may cause an initial tachycardia (47) and may even induce certain dysrhythmias (37,109). Dysrhythmias characterized by heart block, premature ventricular contraction, and tachycardia have been noted with anticholinergic and α_2-agonist combinations, especially if the anticholinergic is administered concurrently rather than prior to the α_2-agonist (47,109,151). Sustained increases in heart rate decrease myocardial oxygen supply and increase myocardial oxygen demand (160). Atropine or glycopyrrolate given before, simultaneously, or after medetomidine (30 to 60 μg/kg BW) resulted in heart block, premature ventricular contractions, and tachycardia (108). Preemptive administration of atropine in medetomidine-sedated dogs induced hypertension and pulsus alternans, an alternating strong and weak pulse, which suggests cardiovascular compromise in human medicine (37). Glycopyrrolate was more effective and produced fewer undesirable side effects when given prior to romifidine in dogs; when the anticholinergic was administered concurrently with romifidine, a rapid decrease in HR with variable atrioventricular (AV) conduction, followed by a period of tachycardia, was noted (47). Therefore, concurrent administration of the anticholinergic with the α_2-agonist is not recommended (47,109).

The significance of this anticholinergic-induced increased HR in the face of the α_2-agonist-induced hypertension in domesticated animal species cannot be quantified or ruled out, especially in those patients with cardiovascular disease, due to the potential for an increase in myocardial workload and oxygen demand. However, the above disadvantages of anticholinergic use must be weighed against its potential advantages; namely, an improvement in cardiac output (although not normalized), a reduction in the frequency of bradyarrhythmias, a decrease in central venous pressure (CVP), and potentially improved tissue oxygen delivery (47). These advantages appear greatest when the anticholinergic is administered with a lowered dose of the α_2-agonist.

When making clinical decisions, it is important to consider the use of anticholinergics with α_2-agonists in 2 situations; when the α_2-agonist is used alone as a sedative, and when the α_2-agonist is used as a premedicant prior to induction and maintenance with propofol or an inhalation anesthetic that promotes vasodilation. The reduction in HR that occurs when an α_2-agonist is used alone is a normal response, and in this situation, high HR working against the high systemic vascular resistance may increase myocardial workload. This is most likely to become clinically significant in cardiovascular compromised patients, when high doses of α_2-agonists are used, or when both situations are present. The peripheral vasodilation that occurs with certain injectable or inhalation anesthetics will offset the α_2-agonist-induced increase in blood pressure from vasoconstriction, and it does make physiologic sense to treat bradycardia in this situation with an anticholinergic. In this situation, the combination of medetomidine with other sedative drugs, such as opioids, may promote a more profound vagally mediated bradycardia in which anticholinergic treatment would be indicated.

Further research is required in these areas to fully clarify the effects of the use of α_2-agonists and anticholinergics with various anesthetic regimes that promote vasodilation or significantly increase vagal tone. At this time, routine use of anticholinergics with sedative doses of α_2-agonists does not appear to be beneficial and may even be detrimental. Concurrent administration of anticholinergics and α_2-agonists is not recommended. Overall, in any emergency situation with the use of medetomidine alone or as a premedicant to general anesthesia, reversal with atipamezole is the most appropriate treatment.

Clinical use of medetomidine

Medetomidine is the most potent α_2-agonist available for use in veterinary anesthesia, since it induces a longer duration of sedation and analgesia compared with xylazine. These characteristics likely make medetomidine the overall best choice for small animal clinical use. Medetomidine is marketed only as a sedative-analgesic agent to facilitate clinical examinations; clinical procedures; minor surgical procedures, with the exception of those requiring muscle relaxation; and minor dental

procedures, where intubation is not required in healthy exercise tolerant dogs. It is contraindicated in dogs that are debilitated; in shock; or stressed due to extreme heat, cold, or fatigue; as well as in dogs with cardiovascular, respiratory, liver, or renal dysfunction.

The recommended label dose of medetomidine as a sedative-analgesic in dogs is 750 μg/m^2 IV, or 1000 μg/m^2, IM, which is equivalent to approximate doses of 20 μg/kg BW, IV, and 40 μg/kg BW, IM, respectively. Typical label sedative doses are as follows: dogs 10 to 20 μg/kg BW, IV; 20 to 40 μg/kg BW, IM; cats 10 to 40 μg/kg BW, IV; 40 to 80 μg/kg BW, IM. Sedation develops within 1 min after IV administration and within 5 min after IM administration. The lower dose is preferred for IV use. Within this range, medetomidine induces the desired sedation, analgesia, and muscle relaxation, but endotracheal intubation is typically not tolerated. At 30 μg/kg BW, IM, medetomidine induces sedation that lasts approximately 70 to 90 min (82). Clinically, it is also important to realize that high doses of medetomidine ($>$ 80 μg/kg BW) will not result in a greater degree of sedation, but they will prolong the duration of sedation and adverse cardiovascular effects (82). In addition, lower doses of medetomidine ($<$ 10 μg/kg BW, IM) alone do not always result in the desired degree of sedation or a reduction in the frequency and severity of adverse effects (29,36).

Currently, the cardiovascular alterations induced by medetomidine are the most problematic effects produced, and they usually preclude its use in critical and cardiovascular compromised patients in veterinary medicine. Despite the obvious negative cardiovascular effects, α_2-agonists are increasingly being utilized in human anesthesia to improve hemodynamic stability, alleviate stress, prevent tachyarrhythmias, and reduce shivering (7,161,162). There are obvious discrepancies in the negative and positive cardiovascular effects of α_2-agonists in veterinary and human patients, in addition to the differences in species, economics, and sophistication of anesthesia.

A primary difference between how α_2-agonists are used in animals and humans is simply an issue of dose. The doses used in humans are much lower than label dose ranges in animals. While there may be obvious species differences, lower doses of α_2-agonists are usually adequate in veterinary species when they are used in combination with other sedatives, and they are already being used with considerable success in many practices as sedatives or preanesthetics. Decreased doses of medetomidine ranging from 2 to 10 μg/kg BW have been combined with various preanesthetics (butorphanol, oxymorphone, hydromorphone, buprenorphine, meperidine, midazolam) to enhance sedation and analgesia, while potentially reducing the duration of the adverse cardiovascular effects associated with its use. Although lowered doses of medetomidine will not prevent cardiovascular and respiratory depression (29), it will promote greater patient safety when used alone or in combination with injectable and inhalant agents.

Summary

Medetomidine is the newest and most specific α_2-agonist licensed for use in dogs to achieve sedation, analgesia, and muscle relaxation. In addition to these desirable effects, a variety of other pharmacologic responses can occur due to α_2-receptor activation in a variety of nontargeted tissues. The cardiovascular alterations induced by medetomidine are the most problematic side effects and usually preclude its use in critical and cardiovascular compromised patients. Additive cardiopulmonary dysfunction may occur when medetomidine is used in combination with other CNS depressants.

Anticholinergic premedication will not fully reverse all of the negative cardiovascular effects associated with medetomidine or other α_2-agonists, and it may promote tachycardia, hypertension, and an increase in myocardial workload in dogs and cats. Although not ideal, healthy animals will likely tolerate the cardiovascular changes associated with anticholinergics and medetomidine. Concurrent administration of anticholinergics and α_2-agonists is not recommended due to the increased frequency of dysrhythmias.

Appropriate case selection is important at any dose of medetomidine in dogs or cats. The use of lower doses of medetomidine, alone or with other anesthetic agents, in combination with oxygen administration, appropriate monitoring, and reversal with atipamezole, where indicated, will promote greater patient safety. Overall, the future successful use of medetomidine in clinical practice for sedation, analgesia, and preanesthetic medication will continue to involve lowered doses and combinations with other sedatives to promote a balanced anesthetic technique. CVJ

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BOOK REVIEW

COMPTE RENDU DE LIVRE

Gilbert FF, Dodds DG. ***The Philosophy and Practice of Wildlife Management, 3rd Edition.*** Krieger Publishing Company, Malabar, Florida, USA, 2001. 355 pp. ISBN 1-57524-051-3. US$64.00.

Wildlife management is the sum of activities, policies, cultural practices, and laws and rules of governments and private citizens whereby a society provides for itself the amount and kind of wildlife that meets its perceived needs. *The Philosophy and Practice of Wildlife Management,* written by 2 well-known Canadian wildlife professionals of long experience, provides a broad overview of this many faceted field in which facts, history, and wisdom are interleaved in a manner that is both interesting to read and insightful. The book is aimed at the young biologist contemplating an education and career in wildlife management. However, it is worthwhile reading for a much larger audience, including veterinarians with professional or avocational interests in wild animals. It is not a "how to" book or training manual, but rather a review and contemplation of the global human enterprise with respect to wildlife.

The book consists of an introduction, 12 chapters and an epilogue. Throughout, the focus of the book is wildlife management of vertebrate animals in Canada and the United States. The coverage of Canada is exceptionally thorough. The sequence of chapters is logical and helpful for those reading the book from beginning to end, but each chapter can be understood independently from the others, making this a useful reference book for the topics covered.

Chapters 1 through 3 review the history and evolution of the practice of managing wild animals and of the societal values that have shaped that practice, including those of aboriginal peoples in North America. Chapters 4 through 9 cover the aspects of animal biology, including disease (a full chapter), that generally have proved to be important in determining management approaches and possibilities, as well as the full range of actual approaches that are taken in managing wildlife: managing habitat, managing individual species, and managing on the basis of societal demand. The 3 final chapters address management issues associated with endangered species, the history and nature of environmental impact assessment; international issues, including management approaches that differ markedly from those in use in North America; and the complexities of wildlife management in developing countries with burgeoning human populations.

The authors are personally dedicated to wise use, conservation, and perpetuation of wild species and their habitats into the future. Nonetheless, they generally are balanced and fair to all parties in their treatment of the many complex management issues that they cover. They urge the reader to fully understand all sides in a dispute and the perspectives of the differing parties. But they also urge wildlife biologists to be unrepentant and indefatigable advocates for wildlife and to recognize this as their particular social and professional obligation.

This is the 3rd and final edition of this book; the authors state there will be no 4th edition. Some parts of it have been fully updated to about 1997, while other parts clearly reference earlier events and times. It is easy to find small annoyances in the book associated with this uneven updating; for example, some of the disease accounts are quite dated. However, this is to quibble over trivia. For veterinarians, it is exhilarating to find a full 42 pages, 12% of the book, dedicated to disease as a critical biological factor in wildlife management. Throughout, the broad picture that the authors portray is the essence and excellence of the book, and this picture is not affected much by small details that do not square with the latest molecular findings.

The book ends on an ominous note of near despair. In the epilogue, the authors express their anguish that the press of human population expansion, with its attendant expropriation of all possible lands and resources, will eliminate their profession and their life's work by eliminating any possibility of wildlife management and conservation. Demographic arithmetic and all current trends are distinctly in this direction. There is an intergenerational pathos in this closing sentiment, wise warriors at the end of long years of hopeful hard work in the trenches scanning a bleak horizon and fearing for the welfare of their youngest comrades in arms and the cause they serve.

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