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REVIEW

A Review on the Current Use of Alpha$_2$ Agonists in Small Ruminants

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Summary

In recent years, alpha$_2$ agonists are the most widely used as sedative and analgesic drugs in veterinary medicine because of several useful properties like fast onset, reversibility and analgesia. Alpha$_2$ agonists produce different actions by binding to their corresponding receptor subtypes located on various parts of the central nervous system. Ruminants are especially sensitive to alpha$_2$ agonists due to the distribution of the specific alpha$_2$ adrenoceptor subtypes, compared with other species. In ruminants, alpha$_2$ agonists are generally used as sedatives and analgesics for restraint, clinical diagnosis, and minor surgeries. Clinical experiments indicated that analgesia does not exist throughout the period of sedation, so these agents alone are not sufficient for painful or major surgical procedure. Epidural administration of alpha$_2$ agonists produced potent analgesia with minimal sedative or cardiovascular effects, and considered one of the most reliable techniques in ruminant. Alpha$_2$ agonists also used as a preanesthetic medication and have been obviously anesthetic sparing effects. They causes some unwanted effects, such as excessive saliva, bradycardia, depressed respiratory rate, decreased rectal temperature, hyperglycemia, uterine contractions and decreased ruminal and intestinal motility. These side effects are influenced by the doses and administration routes of alpha$_2$ agonists, and their selectivity to alpha$_2$ adrenoceptor subtypes. Attentions should be taken to avoid the use of these agents in sick patients, while careful monitoring of the patient condition is always mandatory after receiving these agents. Fortunately, the availability of specific antagonists assures the uses of alpha$_2$ agonists in ruminants. For the safety, an appropriate low dose of alpha$_2$ agonists is always recommended in ruminants.

Keywords: *Alpha$_2$ adrenergic agonists, Alpha$_2$ receptor, Sedation, Analgesia, Premedications, Anesthesia, Ruminant*

Alfa$_2$ Antagonistlerinin Küçük Ruminantlarda Kullanımı Üzerine Bir Derleme

Özet

Son yıllarda alfa$_2$ antagonistleri çabuk etki, geridönüşebilirlilik ve analji gibi bazı özellikleri nedeniyle veteriner hekimlikte sedatif ve analjezik olarak en yaygın kullanılan ilaçlardır. Alfa$_2$ antagonistleri merkezi sinir sisteminin çeşitli bölgelerinde yer alan ilişkili reseptörlere bağlanmak suretiyle değişik reaksiyonlara neden olur. Ruminantlar diğer türlerle karşılaştırıldığında spesifik alfa$_2$ adenoreseptör subtipleri nedeniyle alfa$_2$ antagonistlerine karşı özellikle sensitiflerdir. Ruminantlarda alfa$_2$ antagonistleri genel olarak zapturapt, klinik tanı ve küçük cerrahiler amacıyla sedatif ve analjezik olarak kullanılır. Klinik deneyler analjezinin sedasyonun süresinin tümü boyunca mevcut olmadığını göstermektedir. Bu nedenle bu maddeler acılı veya büyük cerrahi müdahalelerde tek başlarına yeterli değillerdir. Alfa$_2$ antagonistlerinin epidural uygulanması minimal sedatif veya kardiyovasküler etkiler ile birlikte muhtemel analjezi üretmektedir. Bu uygulama ayrıca ruminantlarda en güvenilir teknik olarak kabul edilmektedir. Alfa$_2$ antagonistleri ayrıca preanastetik uygulama olarak da kullanılmaktadır ve bariz olarak anestetik ajanın az kullanımının sağlayıcı etkileri vardır. Bu ilaçlar fazla salivasyon, bradikardi, azalmış respirasyon oranı, azalmış rektal derece, hiperglisemi, uterus kontraksiyonları ve azalmış rumen ve barsak motilitesi gibi istenmeyen etkilere neden olabilir. Bu yan etkiler alfa$_2$ antagonistlerinin dozuna ve uygulanma yoluna ve alfa$_2$ adrenoseptör subtiplerine karşı seçiciliği ile ilişkilidir. Bu ilaçların hasta hayvanlarda kullanılmasından kaçınma konusunda dikkatli davranılmalıdır ve bu ilaçların alınmasını takiben hastanın durumu daima kontrol edilmelidir. Spesifik antagonistlerin mevcudiyeti ruminantlarda alfa$_2$ antagonistlerin kullanılabilmesinde güvence oluşturur. Güvenlik amacıyla alfa$_2$ antagonistlerinin uygun düşük dozu daima ruminantlarda tavsiye edilmektedir.

Anahtar sözcükler: *Alpha$_2$ adrenerjik agonistleri, Alpha$_2$ reseptör, Sedasyon, Analjezi, Premedikayon, Anestezi, Ruminant*

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INTRODUCTION

General anesthesia (GA) is not commonly used in ruminants as its administration results several side effects such as ruminal tympany, regurgitation of reticuloruminal contents, aspiration of refluxed material or saliva, hypoventilation, hypotension and fluid and electrolyte imbalances. The course of anaesthesia is generally complicated and may even endanger the animal's life. Therefore, more caution should be taken while using GA in ruminants. So far, there are very few anesthetic drugs that are licensed for use in ruminants. Among them, alpha$_2$ agonists are one class of sedative and analgesic drugs widely used in veterinary practices because of several useful properties, including fast onset, reliability, analgesia and reversibility [1].

The alpha$_2$ agonists are non-irritant so it could be administered intravenously (IV), intramuscularly (IM) or sub-cutaneously (SC). Alpha$_2$ agonists facilitate the restraint of animals for minor surgical and diagnostic procedures as well as reduced the requirements of injectable and inhalant agents [2].

The sedative and analgesic effects exerted by alpha$_2$ agonists are due to binding to their corresponding receptors. With the development of the molecular biological techniques, numerous subtypes of alpha$_2$ adrenoreceptors (alpha$_{2A}$, alpha$_{2B}$, alpha$_{2C}$, and alpha$_{2D}$) have been found, which developed the knowledge for selective agonists and antagonists. Xylazine hydrochloride is an alpha$_2$-agonist firstly used in ruminant anesthesia. In recent years, detomidine, medetomidine and dexmedetomidine have been reported to use in ruminants for sedation and analgesia [3-5]. Because of variation in the distribution, subtypes of the alpha$_2$ adrenoceptor and their affinities to corresponding ligands, each alpha$_2$ agonists causes dissimilar physiologic effects, including sedation, analgesia, muscle relaxation and unwanted effects (excessive saliva, bradycardia, hypotension, depressed respiratory rate, decreased rectal temperature, hyperglycemia, uterine contractions, decreased ruminal and intestinal motility, and increased urination frequency [5]. In addition, its doses and routes are key factors influencing these effects [6]. Fortunately, the development of specific antagonists expands the safety margin of alpha$_2$ agonists and hence there is an increasing interest to the use of alpha$_2$ agonists in ruminants [7,8].

The purpose of the article is to provide an overview of the main physiological effects of alpha$_2$ agonists and to give a summary of the current scientific and clinical uses of these agents in ruminants.

ALPHA$_2$ ADRENOCEPTOR SUBTYPES AND THEIR AGONISTS

Alpha adrenoreceptors are found in both the central nerve system and peripheral tissues. According to nerve synaptic distribution, they are divided into two subtypes alpha$_1$ and alpha$_2$. Alpha$_1$ adrenoreceptors are found mostly postsynaptically. Alpha$_2$ adrenoreceptors, typically sited presynaptically and can also occur postsynaptically. Alpha adrenoreceptors are bound and activated by their corresponding ligands (alpha$_1$ and alpha$_2$ adrenoceptor agonists). In the central nervous system, alpha$_1$ adrenoreceptor agonists bind to alpha$_1$ receptors, and exert excitatory functions (arousal, restlessness, increased locomotors activity) [9], while alpha$_2$ adrenoreceptor agonists bind to alpha$_2$ receptors which mainly produce inhibitory functions. The beneficial physiological effects of alpha$_2$ adrenoreceptor agonists include sedation, analgesia and muscle relaxation [1].

The alpha$_2$ agonists like as xylazine, detomidine, medetomidine and dexmedetomidine are clinically licensed for use in animals while clonidine and romifidine are available only for human. Clinically, the degree of sedation and analgesia produced by alpha$_2$ agonists are related to the individual selectivity and affinity of alpha$_2$ agonists between the alpha$_1$ and alpha$_2$ receptor binding sites. The order of alpha$_1$ and alpha$_2$ selectivity for alpha agonists are medetomidine (1620:1), detomidine (260:1), clonidine (220:1), romifidine (340:1) and xylazine (160:1) [10]. Studies have demonstrated that central alpha$_1$ adrenoceptor stimulation antagonizes the hypnotic response to even potent alpha$_2$ agonists, such as dexmedetomidine, and that the alpha$_1$ adrenoceptor effects will predominate with increased or toxic doses of alpha$_2$ agonists. With the advent of the molecular biological techniques, numerous alpha$_2$ adrenoceptor subtypes are found. These include alpha$_{2A}$, alpha$_{2B}$, alpha$_{2C}$, and alpha$_{2D}$ [11,12]. Alpha$_{2A}$ receptors are most prevalent in the CNS, whereas alpha$_{2B}$ receptors are most prevalent peripherally. Alpha$_{2A}$, alpha$_{2B}$, and alpha$_{2C}$ receptors are thought to be involved in the analgesic actions of alpha$_2$ agonist drugs. Different species have different receptor subtypes, distributions and receptor densities [10].

In the CNS, alpha$_2$ agonists are responsible for different actions after binding to their corresponding receptor subtypes. The diversity in alpha$_2$ adrenoceptor subtypes and distribution has led to considerable differences in dose and overall effects of alpha$_2$ agonists in the various species. For example, alpha$_{2A}$ subtype predominated in canine and rat brainstems while the alpha$_{2D}$ subtype appears to predominate in the sheep brainstem [13,14]. Perhaps, this difference in subtypes gives an explanation why ruminants have greater sensitivity to alpha$_2$ agonists requiring less dose to produce the sedative effects as compared to other species [15].

USES OF ALPHA$_2$ ADRENERGIC AGONISTS

The use of alpha$_2$ agonists in veterinary practices

were first reported in late 1960 [16] and revolutionized for sedation and analgesia, particularly in large animals. Since then, alpha$_2$ agonists have been used for profound sedation and analgesia [5].

Sedative Effects

The interests in the use of alpha$_2$ agonists in veterinary practices are related to the ability of these drugs to produce reliable sedation and anxiolysis. These effects are mediated by the activation of the alpha$_{2A}$-adrenergic receptor subtype found in the locus coeruleus neurons in the pons and lower brainstem causing a decrease in norepinephrine release [17-19]. Centrally, norepinephrine is necessary for arousal. If the release of norepinephrine is blocked, the net result is sedation. Sometimes, failure to achieve deep sedation may be due to preexisting stress or pain and excitement, because all of these conditions increase endogenous catecholamine levels that interfere with the alpha$_2$-agonist-induced reduction of excitatory neurotransmitter release. In animals, the sedative effect is well achieved, when these agents are given in calm and quiet surroundings with minimal environmental stress [20].

The behavioral events are similar for goats administered any of the alpha$_2$ agonists, and include an initial appearance of nervousness followed by lowering head, protrusion of the nictitating membrane and tongue, partial drooping of the eyelids, and animals rapidly become ataxic [18]. There is generally a reduced awareness of the environment, although a response may occur to stimulation such as noise or touch. For all the drugs, the onset of sedation is slower following intramuscular administration [21-24].

Ruminants have a remarkable alpha$_{2D}$-adrenergic receptor, which makes them sensitive to the sedative effects. Several workers have investigated the effect of medetomidine in ruminants. The sedative effects were noted in 9 min and lasted for 90-120 min after administration of medetomidine (40 µg/kg, IM) in sheep [21]. The sedative effects of xylazine (0.1 mg/kg) and detomidine (50 µg/kg) in goats was observed with maximal effect within 5 to 12 min, and lasted for 77 to 85 min respectively [5].

Analgesic Effects

Alpha$_2$ agonists produce analgesia by stimulating receptors within the brain and spinal cord [22]. Studies showed that alpha$_2$ agonists bind with the receptors in the substantia gelatinosa of the dorsal horn of spinal cord [25] and in the brainstem, where modulations of nociceptive signals are likely to be started [26]. It is further indicated that presynaptic and postsynaptic inhibitory effect of alpha$_2$ agonists are responsible for antinociceptive action [27].

The modulation of pain is also involved in an interaction between alpha$_2$ adrenoreceptors and opiate receptors in brain and spinal cord [28,29]. Alpha$_2$ and opioid receptors are found in similar regions in the brain (even on same neurons), and inferred to share common molecular machinery beyond the receptors. Alpha$_2$ agonists or opioid agonists bind to their receptors, and activate signal transduction systems (membrane associated G proteins), which induces a chain of events that open potassium channels in the neuronal membrane. Activation of these channels in the postsynaptic neurons leads to hyperpolarization of the cells, which ultimately makes the cells unresponsive to the excitatory input and effectively blocks the pain pathway [9]. Consequently, the alpha$_2$ agonists and opioid agonists produce analgesia by similar mechanisms [9,23].

Clinical experiments indicate that analgesia does not exist throughout the entire period of sedation, and these agents alone are incompatible for painful or major surgical procedure. It is important to note that the analgesic effects last for half the duration of the sedation. Shah *et al.*[5] observed sedation after IV administrations of xylazine and detomidine in goats are 77 min and 85 min while skin analgesia remained only for 40 min and 33 min respectively. The analgesic effect produced by medetomidine is more profound and longer than that mediated by xylazine. The therapeutic response of alpha$_2$ agonists for the treatment of acute and chronic pain has been demonstrated as their usefulness by parenteral and epidural route [30,31].

Epidural administration of alpha$_2$ agonists produced potent analgesia by activation of alpha$_2$ adrenergic receptors ($\alpha_{2A/D}$, α_{2C}) in the substantia gelatinosa of the dorsal horn in spinal cord and inhibits the release of norepinephrine [32]. It has minimal sedative or cardiovascular effects [33] and considered as one of the most reliable techniques for regional analgesia in calves, sheep and goats for all surgical procedures caudal to the umbilicus [34,35].

Several alpha$_2$ agonists have been epidurally or sub-arachnoidly used for analgesia. It is reported that epidural administration of xylazine causes profound analgesia, relaxation of constrictor vulvae muscle, anal sphincter and urinary bladder [18,36]. Prado *et al.*[37] indicated that detomidine caused perineum and flank analgesia in cattle. Tranquilli *et al.*[38] used xylazine (0.05 mg/kg) or medetomidine (0.01 mg/kg) subarachnoidly in goats, and found the sensory blockage of nociceptive impulses for more than 2 h. However, their absorption from epidural space has apparently causes cardiopulmonary depression in the ruminants. Epidural administration of clonidine did not affect regional blood flow to the spinal cord in sheep [39]. Romifidine produced mild to moderate degrees of hindquarter analgesia within 5.2 min in goats when administered epidurally [40]. But this effect persisted shorter than intrathecal injection of xylazine (0.05 mg/kg) and medetomidine (10 µg/kg) in goats [41].

Epidural administration of alpha$_2$ agonists, alone, or in combination with local anesthetics causes bradycardia, respiratory acidosis, reduced ruminal motility, and increased urination frequency [6,42-44]. These side effects

are generally well tolerated by young, healthy animals while significant morbidity and mortality may occur in patients having poor cardiopulmonary functions [6]. However, at appropriate dose, epidural anesthesia-with local anesthetics produces minimal hemodynamic and respiratory changes in conscious animals [35].

Anesthetic Sparing Effects

Alpha$_2$ agonists as a preanesthetics medication have been obvious anesthetic sparing effects for injectable as well as inhalant agents. However, these effects are associated with the affinity of the drugs for the alpha$_2$ adrenoreceptors [45]. That is, more specific to the alpha$_2$ agonists, and betters the anesthetic sparing effect [46].

Xylazine as a preanesthetics can reduce the amount of anesthetics (such as thiopental) required by 25% to 50% of the original dosage. This decrease depends upon the dose of xylazine, species, and the speed with which the anesthetic is given. The dose level of 0.04-0.6 mg/kg IV of xylazine is usually given prior to 2.2 to 4.4 mg/kg of IV ketamine in sheep and goats. This has resulted in satisfactory induction of anesthesia persisting for 10-15 min [6,15]. The amount of halothane requirements for anesthesia (MAC) is reduced nearly by 40% and that of barbiturate reduced by one-third to be one-half of the estimated doses when xylazine is used as premedication [46]. One another study reported premedication of xylazine lead to 50% of a reduction in methohexital dose [47]. As premedication, romifidine (20 µg/kg) reduced the induction dose of propofol by 60% [48], and medetomidine (1 µg/kg/IV) reduced 38% of induction dose of propofol [49]. Although alpha$_2$ agonists and inhalant anesthetics do not share common receptors, as demonstrated by the inability of alpha$_2$ antagonists to reverse halothane anesthesia. However, a synergism may exist between these agents, since both increase potassium conductance and induce neuronal hyperpolarization in the brain [50].

SIDE EFFECTS OF ALPHA$_2$ AGONISTS

Cardiovascular Effects

The cardiovascular effects of all alpha$_2$ agonists include bradycardia and associated bradyarrhythmia (1st and 2nd degree atrioventricular heart block), a dramatic reduction in cardiac output by up to 50% (L blood/min), and an increase in systemic vascular resistance [51,52]. Several mechanisms contribute to induce bradycardia, including a decrease in sympathetic outflow from CNS, the direct depression of cardiac pacemaker and conduction, the inhibition of norepinephrine release from sympathetic nerve terminals, and an increase in the release of acetylcholine from parasympathetic nerves in heart [53,54]. Systemic vascular resistance is due to vasoconstriction in response to stimulation of alpha$_2$ receptors on the vascular smooth muscles. The decrease in cardiac output is initially concerned to baroreceptor reflex and central sympatholytic action leading decreased heart rate. Alpha$_2$ agonists also affect receptors exiting in the heart and blood vessels resulting significant cardiovascular side effects. These effects of alpha$_2$ agonists are mainly dose- and route-dependent, although IM administration of drug has less effect as compared to IV. The increases in arterial blood pressure, which is typically dose related particular with the higher dose, caused a more pronounced stimulation of peripheral adrenoreceptors and vasoconstriction [51,52]. The initial hypertension is greater when the alpha$_2$-agonist is administered IV and there is a 26% increase in MAP after IV administration of medetomidine or xylazine as compared to an 18% increase when the same doses were administered intramuscularly. The differences in the initial blood pressure response with different routes are likely related to variations in the speed of uptake and absorption of the drug on the overall effect at the peripheral adrenoreceptors [55]. Based on these findings, it is recommended that lowered doses of alpha$_2$-agonists when administered IM, avoid extremes of blood pressure [24,55].

Xylazine in sheep has minor cardiovascular side effects at the dose of 0.15 mg/kg IV, while at 0.5 mg/kg IV decreased heart rate by 25% and cardiac output by 37% and retained up to 1 h. Xylazine (0.05 mg/kg IM) caused only minor cardiovascular changes [56]. Jansen *et al.*[57] reported that xylazine (0.2 mg/kg IM) in pregnant ewes decrease maternal (30%) and fetal (20%) heart rate. The specific alpha$_2$ agonists, i.e. dexmedetomidine, indicate a beneficial effect of alpha$_2$ agonists in high-risk patients. In one clinical trial in human, it is confirmed that peri-operative administration of dexmedetomidine reduced a plasma catecholamine level by 90%, and thereby decreased intra-operative hypertension and tachycardia compared with placebo [58].

Premedication with atropine has been shown to prevent the 2nd degree heart block [59], however, the use is rather controversial, because atropine blocks transmission of vagal impulses to the heart, animals with a preexisting high vagal tone would show a relatively greater tachycardia than those with low vagal tone. Cardiac output tends to increase with atropine primarily because of the increase in heart rate. Large doses of atropine are directly depressant to the myocardium and also cause cutaneous dilation as a result of a direct vascular smooth muscle effect [15].

Alpha$_2$ agonists should not be used in animals with compromised cardiac output, such as preexisting heart disease, especially those with Brady arrhythmia, poor myocardial contractility, obstructive valvular disease, dehydration, hypovolemia, or sepsis. Attentions should be taken to avoid these agents in geriatric, pediatric, pregnant or diabetic patients. Careful monitoring of the patient's condition is always important after receiving these agents.

Fortunately, reversing agents are available to antagonize the adverse effects [60-63].

Respiratory Effects

Almost all alpha$_2$ agonists cause some respiratory side effects, due to secondary depression of CNS [51,60]. The respiratory effects are species specific [61,64]. In ruminants, alpha$_2$ agonists can cause bronchoconstriction and an increase in pulmonary vascular resistance, leading to pulmonary edema and impaired oxygenation of blood with resultant hypoxaemia. Care must be taken when used in ruminants, especially small ruminants [10]. In sheep, xylazine can cause rapid increases in respiratory rate, airway pressure, and pulmonary elastics with slight changes in $PaCO_2$. Hypoxemia is frequently observed, terminating in fulminant pulmonary edema and death. Within 3 min after administration, sheep have activation of pulmonary intravascular macrophages, and interstitial and alveolar edema [65].

Dexmedetomidine decreases respiratory rate in sheep and goat [66]. Several investigations have demonstrated a mild to severe decrease in arterial PO_2 [67]. The decrease in arterial oxygenation may be gradual and not recognized until the animal collapses. Alpha$_2$ agonists decrease the gastrointestinal motility, resulting in bloat, which further impair ventilation. Acute pulmonary edema, manifested as wheezy, labored breathing, has been reported in sheep 15 min after injection of xylazine [68].

The irregular breathing and reduced ventilation rate have been observed after epidural administration of a lower dose of alpha$_2$ agonists [36,41]. Researchers reported tachypnea, dyspnea and transient apnea followed by irregular and deep breathing in goats and other species. Besides these, there were a concurrent decrease in tidal volume in sheep and goats [20,69,70]. Administration of alpha$_2$ antagonists reversed the sedation however the respiratory effects were not completely abolished [60,62].

Other Side Effects of Alpha$_2$ Agonists

Alpha$_2$ agonists cause hyperglycemia, increase uterine contractions which may lead to premature abortion, and a decrease in intestinal motility. They inhibit sympathetic outflow and modulate the stress response to anesthesia and surgery. Alpha$_2$ agonists cause hyperglycemia by direct inhibition of insulin release from β-cells within the pancreas [71,72], increased production of glucose by the liver or a rise in adrenocortical hormones due to stress [73]. Alpha$_2$ agonists also increase growth hormone secretion, which may be contributed to the hyperglycemic effect. Polyuria is reported in goats within 20 min and continued till 70 min after xylazine administration (0.1 mg/kg) [74]. Mohammed and Yelwa, reported that polyuria is associated with hyperglycemia [70].

Alpha$_2$ agonists can cross the placenta, increase uterine blood flow and contraction by stimulating alpha$_2$ adrenoreceptors. Due to high lipid content, they may be partly trapped in the placenta. So there is a tiny amount in the fetal circulation. The effect of drugs to stimulate alpha$_2$ adrenoreceptors depend on estrogen which increase sensitivity of the alpha$_2$ adrenoreceptors; a high level of progesterone during pregnancy increases the sensitivity of alpha$_2$ adrenoreceptors and actually decreases the contractility of the uterus [75]. Xylazine like oxytocin causes contraction of the bovine uterus [32]. There has been a report of cows going into premature labor [76].

ANTAGONISM

Alpha$_2$ adrenergic receptor antagonists are used primarily in veterinary medicine to reverse the effects and expand the safety margin of alpha$_2$ agonists. Atipamezole, yohimbine, tolazoline and idazoxan are antagonists used commonly in ruminants [63,73].

The beneficial effects of atipamezole or yohimbine come from their specific alpha$_2$ adrenoceptor antagonist action in goats and sheep [77,78]. In sheep, yohimbine (0.2 and 0.4 mg/kg/IV) is effective to prevent bradycardia induced by xylazine [79]. Atipamezole a more potent having alpha$_2$ and alpha$_1$ selectivity with a ratio of 200:300 times higher than yohimbine requiring a lower dose [80]. Therefore, atipamezole is useful for antagonizing the CNS depressant effects of medetomidine in goats [81].

The combined uses of two kinds of alpha$_2$ adrenoceptor antagonists have better reversal effect. Atipamezole (0.2 mg/kg) and yohimbine (0.2 mg/kg) administration in goats significantly reduced recumbency period and stand within 1 min. Kinjavdekar *et al.*[82] reported that yohimbine (0.25 mg/kg IV) and atipamezole (0.005 mg/kg IV) antagonize the epidural effect of medetomidine (0.01 mg/kg) in goats. Tolazoline is an imidazole derivative (alpha$_1$ and alpha$_2$) adrenoreceptor antagonist and considered as a useful antagonist for sedation and side effects induced by xylazine in various species [23].

All alpha$_2$ antagonists cause CNS excitement, vasodilation and tachycardia. Therefore alpha$_2$ receptor antagonist should be given slowly to minimize adverse effects. Alternatively, a fractional dose may be given slowly IV and the rest through IM to minimize side effects [15].

CONCLUSION

Alpha$_2$ agonists are commonly used in veterinary practices for sedation, analgesia and muscle relaxation. The pharmacological activities of all alpha$_2$ agonists are almost similar, but some differences exist due to their selectivity for specific receptors. Alpha$_2$ agonists are routinely used in combination with other anaesthetic agents to reduce dose and side effects of the other agents.

Physiological alterations induced by alpha$_2$ agonists totally depend on its dose and route, and used alone or in combination with other sedatives or anesthetics. The lowest possible dose required to achieve the desired depth and duration of action for a given procedure should be used. When these factors are appropriately considered, the risks caused by alpha$_2$ agonists can be minimized. Alpha$_2$ antagonists produced reversal effects for sedation, CNS depression and cardiopulmonary changes induced by alpha$_2$ agonist. It is concluded that alpha$_2$ agonists are safe to use in ruminant in a field as well as hospital conditions.

Conflict of Interest Statement

The authors declare that they have no financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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