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REVIEW

Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog

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Abstract

Alpha$_2$-adrenoreceptor agonists (α_2-agonists) are commonly used in small animal anaesthesia for their potent sedative and analgesic properties, although concerns about their cardiovascular effects have prevented their full adoption into veterinary practice. Research into alpha$_2$ adrenoreceptor agonists and their clinical use is extensive, therefore this review focuses on the use of dexmedetomidine and medetomidine in dogs. Emphasis is given to the cardiovascular effects and antinociceptive action of these agents.

Keywords α_2-agonist, antinociception, cardiovascular, dexmedetomidine, dog, medetomidine.

Introduction

Despite their widespread clinical use, concerns about the cardiovascular effects of α_2-agonists have prevented their full adoption into veterinary practice. A previous UK study (Clarke & Hall 1990) indicated that anaesthesia involving xylazine was linked with a high mortality rate compared with anaesthesia techniques from which it was excluded. When only ASA 1 and 2 dogs were considered, one dog in 60 that received xylazine as part of the anaesthetic died, compared with an overall death rate of one in 870 dogs. However the total number of dogs that received xylazine in this survey was low (152 animals). A prospective epidemiological study is in progress investigating anaesthetic mortality and morbidity in British small animal practice (Brodbelt et al. 2002). This may provide data about anaesthetic risk when α_2-agonists such as medetomidine are incorporated into the anaesthetic technique. Research into α_2-agonists and their clinical use is extensive, therefore this article focuses on the use of dexmedetomidine and medetomidine in dogs. Emphasis is given to a review of the cardiovascular effects and antinociceptive properties of these agents. Throughout the article, many references are made to the effects of dexmedetomidine or medetomidine given at specific doses. Therefore, for the purpose of comparison, it is emphasized that the data sheet dose range for medetomidine as pre-anaesthetic medication is 10–40 μg kg^{-1} (IV, IM, or SC) in dogs. In the UK, Pfizer Animal Health recommend a dose of 10 μg kg^{-1}.

The α_2-agonist medetomidine is an equal mixture of two optical enantiomers, dexmedetomidine and levomedetomidine. The latter is generally considered to be pharmacologically inactive (MacDonald et al. 1991). The selectivity of the active isomer

dexmedetomidine is greater for the α_2-receptor than the α_1-receptor, compared with the racemate (Aantaa et al. 1989). The alpha$_2$-adrenoreceptor (α_2-receptor) is a transmembrane G protein coupled receptor (Khan et al. 1999) found pre-, post- and extrasynpatically in different tissues (Paton & Vizi 1969; Wikberg 1979). Three different isoreceptors have been defined in terms of affinity for alpha adrenoreceptor ligands alpha-2a, -2b and -2c (Bylund 1985). These subtypes bind α_2-agonists and antagonists with similar affinities. A number of different G protein coupled effector mechanisms of α_2-receptors have been characterized, although the physiologic and clinical relevance of these different pathways remains to be elucidated. The most important consequence of α_2-receptor stimulation is inhibition of adenylyl cyclase, resulting in decreased formation of cAMP, an important regulator of cellular function. Alternative effector mechanisms include activation of G-protein gated potassium ion channels, causing neuronal cell hyperpolarization, which may contribute to the decreased excitability of CNS neurons following α_2-agonist administration and sedation (Aghajanian & VanderMaelen 1982). Alpha$_2$-receptor stimulation resulting in inhibition of neurotransmitter release is mediated through a decrease in calcium ion conductance, involving direct regulation of calcium entry by voltage-gated calcium ion channels (Lipscombe et al. 1989).

Post-synpatic α_2-receptors have a distinct physiological function in a number of different tissues including the liver, pancreas, platelets, kidney, adipose tissue and the eye. Pre-synaptic α_2-receptors are present in sympathetic nerve endings and noradrenergic neurones in the central nervous system where, when activated, they will inhibit the release of noradrenaline (Langer 1981). The locus coeruleus (LC) is a small neuronal nucleus located bilaterally in the upper brainstem and is the largest noradrenergic cell group in the brain. It is an important modulator of wakefulness and may be the major site for the sedative action of α_2-agonists, mediated by α_{2a}-receptors located there (Scheinin & Schwinn 1992). A high density of α_2-receptors has also been demonstrated in the vagus nerve, intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains α_{2a} subtype receptors, while the primary sensory neurones contain both α_{2a} and α_{2c} subtypes of adrenoreceptors. Centrally, the subtype α_{2b}-receptor has been found only in the thalamus (MacDonald & Scheinin 1995), although α_{2b}-receptors in vascular smooth muscle are crucial to mediating the peripheral hypertension seen after administration of α_2-agonists (Link et al. 1996). Dexmedetomidine is not a pure α_2 agonist; it is also able to combine with noradrenergic imidazoline receptors (Hieble & Ruffolo 1995). These receptors, specifically recognizing the imidazoline or oxazoline chemical structure, have been classified into I1 found in the brain and I2 found in the brain, kidney and pancreas (Khan et al. 1999). Imidazoline receptor stimulation mediates a central hypotensive (I1) and anti-arrhythmogenic action. Of the other α_2-agonists used in veterinary practice, detomidine also posses an imidazole ring, while xylazine and romifidine do not (Faber et al. 1998). It is possible that some of the effects of dexmedetomidine and detomidine are mediated by imidazoline receptors.

A number of clinical studies have investigated the use of medetomidine for pre-anaesthetic medication in dogs followed by antagonism with atipamezole at the end of anaesthesia to hasten recovery. These confirm that medetomidine is a potent sedative that can be given before anaesthesia with a range of anaesthetic agents including thiopental, propofol, ketamine, halothane and isoflurane. Recoveries from anaesthesia following atipamezole are usually rapid and of good quality (Verstegen et al. 1990; Young et al. 1990; Hellebrekers & Sap 1997; Hellebrekers et al. 1998;) and while extensive cardiovascular monitoring was not performed in all cases, the conclusions of these studies were that medetomidine was safe for pre-anaesthetic medication in 'healthy' dogs in combination with commonly used anaesthetics. The advantages of incorporating an α_2 agonist into the anaesthetic include: the provision of potent sedation and 'background analgesia', a reduction in the amount of other anaesthetics required to produce conditions for surgery (Young et al. 1990; Ewing et al. 1993; Hammond & England 1994), provision of analgesia (Pypendop & Verstegen 1994), and reversibility (Bartram et al. 1994). However in spite of these benefits and the results of clinical studies indicating efficacy and safety in healthy animals, the use of α_2-agonists is not universally supported because of concerns relating to the potent cardiovascular effects of α_2-agonist drugs. In order to confront these concerns, the results of studies examining the haemodynamic effects of dexmedetomidine and medetomidine in dogs must be assessed.

Haemodynamic effects of α_2-agonists

A number of invasive haemodynamic studies have been carried out to investigate the cardiovascular effects of dexmedetomidine in dogs and a significant body of data describing the effects of dexmedetomidine on coronary blood flow and myocardial oxygen demand exists. This results from use of the dog as an experimental model for human beings in relation to the effects of α_2-agonists on myocardial blood flow and oxygenation.

The haemodynamic effects of α_2-agonists in the dog have typically been described as a biphasic blood pressure response with decreased heart rate and cardiac index, increased systemic vascular resistance index and central venous pressure. Minimum changes in pulmonary arterial pressure or pulmonary capillary wedge pressure are usually reported. (Bloor et al. 1992; Pypendop & Verstegen 1998; Kuusela et al. 2000). Pypendop & Verstegen (1998) investigating the dose dependency of these effects in dogs, found that medetomidine caused qualitatively similar haemodynamic changes, irrespective of dose between 1 and 20 μg kg^{-1} IV, although these changes were less at doses of 1 and 2 μg kg^{-1}. Near-maximal cardiovascular effects were present with medetomidine doses as low as 5 μg kg^{-1}, higher doses had little additional effect on cardiovascular function. This demonstrated a limited dose dependency of cardiovascular effects in the dose range studied.

Blood pressure

The initial increase in blood pressure results from peripheral vasoconstriction caused by activation of post-synaptic α_2-receptors in peripheral vascular smooth muscle. This is associated with increased vagal tone and decreased heart rate (phase 1). In human beings, blood pressure then falls as vasoconstriction wanes and a central hypotensive effect predominates (phase 2). Sympathetic nervous tone is decreased, and this phase is associated with a prolonged decrease in heart rate. The exact location and the specific receptors responsible for the central hypotensive effect are unknown. Post-synaptic α_2 and imidazoline receptors in the brainstem are probably involved (Tibirica et al. 1991). In rabbits, clonidine – which is a less selective α_2-agonist than dexmedetomidine – lowers the set point around which arterial blood pressure is regulated and increases the gain of the baroreceptor system. This results in lower heart rates for a given increase in blood pressure (Badoer et al. 1983). The bradycardia commonly seen after α_2-agonist administration during phase 2 may therefore result from a central sympatholytic action which leaves vagal efferent activity unaffected. However, the clinical observation that bradycardia (during phase 2) is often unresponsive to atropine does not fully support this hypothesis. The characteristics of the blood pressure changes appear to be in part determined by dose. Higher doses, i.e. >20 μg kg^{-1} cause longer duration hypertension associated with a persistent increase in systemic vascular resistance (Kuusela et al. 2000). At lower doses, central effects predominate and (carotid arterial) blood pressure decreases to pre-treatment or below pre-treatment values (Pypendop & Verstegen 1998). Alpha$_2$-agonists have not been linked with hypotension in the dog in clinical studies where blood pressure was measured. Pypendop & Verstegen (1998) did not encounter mean arterial pressures <80 mmHg at any dose. Blood pressure remained within an acceptable range in dogs given 10 μg kg^{-1} dexmedetomidine and anaesthetized with either isoflurane or propofol (Kuusela et al. 2003) suggesting that the peripheral vasoconstrictor action of dexmedetomidine predominates during isoflurane and propofol anaesthesia. Other studies have found similar results (Vickery et al. 1988; Bloor et al. 1992; Thurmon et al. 1994; Hellebrekers & Sap 1997; Ko et al. 2000; Kuusela et al. 2000, 2001). These findings may reflect a greater sensitivity of dogs for the vasoconstrictor effect of α_2-agonists compared with human beings, where hypotension is the principle haemodynamic effect (Khan et al. 1999). Doses of dexmedetomidine given during studies in human beings are usually lower than those administered to dogs, therefore dose dependency may also contribute to this observation. However, 1 μg kg^{-1} dexmedetomidine IV in human beings caused no significant change in the systemic vascular resistance index (SVRI) (Ebert et al. 2000), while in dogs, SVRI is transiently increased at the same dose (Pypendop & Verstegen 1998).

Cardiac output

Cardiac output decreases following α_2-agonist administration in dogs (Vickery et al. 1988; Bloor et al. 1992; Flacke et al. 1993; Pypendop & Verstegen 1998). The precise mechanism is unknown although several mechanisms have been suggested, including: (i) direct myocardial depressant effect; (ii) decreased function in response to α_2-agonist-

mediated increase in afterload; and (iii) myocardial hypoxia and dysfunction in response to coronary vasoconstriction.

Direct myocardial depressant effect of dexmedetomidine

Isolated heart studies investigating the direct effects of dexmedetomidine on the canine myocardium consistently demonstrate that dexmedetomidine does not have a direct depressant effect (Housmans 1990; Coughlan et al. 1992; Flacke et al. 1992). That atipamezole consistently and rapidly reversed the myocardial depressant effect of dexmedetomidine in anaesthetized dogs (indicated by a reduction in cardiac index) suggests that the depression is not caused by an α_2-agonist-mediated release of myocardial depressant factors (Flacke et al. 1993).

Myocardial dysfunction as a result of increased afterload

Bloor et al. (1992) proposed that cardiac output decreases in response to dexmedetomidine as a result of the increased afterload resulting from increased systemic vascular resistance (this lowers and 'right-shifts' the Frank-Starling curve for the heart so that cardiac output is lower for a given preload). In one study (Bloor et al. 1992) which investigated the haemodynamic effects of dexmedetomidine in dogs anaesthetized with isoflurane, cardiac output reductions were reversed when nifedipine was given to reduce systemic vascular resistance, and provides evidence for this proposal. In addition, circulating plasma catecholamine levels were reduced to near-undetectable levels after dexmedetomidine: reduced inotropy will limit stroke volume in the face of increased afterload (Bloor et al. 1992). However, increased systemic vascular resistance alone does not account for the degree of cardiac output depression recorded in dogs given dexmedetomidine because numerous studies indicate that the normal canine heart maintains cardiac output when afterload is increased, even when denervated (Seiten et al. 1964; Zanderberg et al. 1984; Woodman & Vatner 1986; Flacke et al. 1992).

Myocardial hypoxia and α_2-agonist induced coronary vasoconstriction

Coronary blood flow is predominantly determined by metabolic, not neurogenic influences. However, both α_1- and α_2-receptors are present in epicardial coronary vessels and their stimulation reduces coronary artery diameter and perfusion under certain conditions. Myocardial hypoxia resulting from decreased coronary blood flow has been investigated as a cause of myocardial dysfunction following dexmedetomidine (Coughlan et al. 1992; Flacke et al. 1993; Lawrence et al. 1996a; Roekaerts et al. 1996b). The direct effects of α_2-agonists on coronary blood flow is a prerequisite to understanding how α_2-agonists affect the relationship between myocardial O_2 availability and extraction and how this may influence cardiac contractility.

Direct effects of α_2-agonists on the coronary vasculature

Coughlan et al. (1992) investigated the direct vasoactive effects of dexmedetomidine on isolated canine coronary arteries and demonstrated that the drug caused atipamezole-reversible vasoconstriction of both isolated proximal and distal coronary arteries. A differential distribution of α_1- and α_2-receptors between proximal and distal coronary arteries has been suggested (Heusch et al. 1984) with α_2-adrenergic sites predominating in distal resistance vessels and α_1-adrenergic effects in the proximal, and larger epicardial arteries. In the study of Coughlan et al. (1992) high-dose dexmedetomidine caused vasoconstriction of proximal coronary vessels that was not antagonized by atipamezole, suggesting that high-dose dexmedetomidine can also stimulate proximal α_1-receptors. The concentration of dexmedetomidine used in this *in vitro* study cannot easily be related to clinical doses. In an *in vivo* study, dexmedetomidine (1 μg kg^{-1}) significantly increased coronary vascular resistance in dogs (Flacke et al. 1993). The myocardium is predominantly dependent on an increase in coronary blood flow to meet increased O_2 demand, as the O_2 extraction reserve of coronary blood flow is small. Therefore, inappropriate coronary vasoconstriction induced by dexmedetomidine might cause myocardial hypoxia.

Effect of α_2-agonists on coronary blood flow

Despite a direct vasoconstrictor effect of α_2-agonists, coronary blood flow remains under a high degree of metabolic control, therefore it is also important to investigate coronary blood flow changes in intact anaesthetized dogs. Flacke et al. (1993) found that

the dexmedetomidine-induced reduction in coronary blood flow in dogs anaesthetized with enflurane was associated with increased coronary vascular resistance and increased O_2 extraction from the coronary blood supply. Roekaerts et al. (1996a) also found dexmedetomidine at doses of 1 and 10 μg kg^{-1} decreased coronary blood flow in all myocardial layers, and that this was associated with an increased coronary vascular resistance, i.e. vasoconstriction. In the same study (Roekaerts et al. 1996a) coronary blood flow was also measured in halothane-anaesthetized dogs after coronary artery occlusion and dexmedetomidine administration, and while reactive hyperaemia normally follows coronary artery occlusion, it was found that dexmedetomidine decreased blood flow in the epicardial layer to pre-occlusion levels. However, hyperaemic responses were not suppressed in the more vulnerable endocardial layer, where post-occlusion ischaemia is usually most severe. This finding is supported by others (Nathan & Feigl 1986; Chilian & Ackell 1988). Therefore, it seems likely that in this model, α_2-adrenergic vasoconstriction was overcome by metabolite-induced vasodilatation which preserved endocardial blood flow. In contrast to anaesthetized animal studies, dexmedetomidine does not effect coronary blood flow in conscious dogs (Schmeling et al. 1991).

The effects of α_2-agonist induced coronary hypoperfusion

The reduction in coronary blood flow identified in previous studies was associated with increased O_2 extraction across the coronary vasculature (Flacke et al. 1993). As the O_2 extraction reserve is small, increased myocardial O_2 demand evokes greater flow under normal conditions and so increased extraction is normally held to indicate significant coronary blood flow reduction. Whether this causes myocardial hypoxia or whether increased O_2 extraction compensates adequately for the decreased flow is unknown. Roekaerts et al. (1996a) found that the reduced coronary blood flow in the normal myocardium after dexmedetomidine was not associated with altered O_2 oxygen and lactate extraction, indicating that myocardial O_2 supply-demand coupling was unaffected. The reduction in blood flow was appropriately related to a reduction in myocardial oxygen demand following dexmedetomidine, primarily resulting from reductions in heart rate and contractility. Lawrence et al. (1996a) studied the effect of dexmedetomidine on myocardial energy requirement and O_2 supply balance in anaesthetized dogs and found that dexmedetomidine decreased myocardial energy requirements and O_2 consumption, which corresponds to a decreased myocardial blood flow and O_2 supply. Increased myocardial O_2 extraction occurred at the highest dose of dexmedetomidine (10 μg kg^{-1}) investigated, suggesting α_2-adrenergic vasoconstriction occurred at this dose. This is equivalent to 20 μg kg^{-1} medetomidine, i.e. the lower end of the data sheet dose for pre-anaesthetic medication. The endocardial: epicardial blood flow ratio also increased, indicating the predominating vasodilatory effects of metabolites in the endocardium compared with the epicardium. A decrease in heart rate also improves endocardial blood flow (Feigl 1983).

It remains difficult to link dexmedetomidine-induced coronary vasoconstriction with myocardial hypoxia and reduced cardiac output. Despite increased afterload (that increases myocardial work) α_2-agonists appear to reduce myocardial O_2 demand. Coronary vasoconstriction occurs in anaesthetized dogs given dexmedetomidine. Some studies suggest that this is not associated with myocardial hypoxia – at least in dogs with normal cardiovascular function.

Alpha$_2$-agonists and tissue oxygenation

It is not known whether the reductions in cardiac output caused by α_2-agonists are detrimental in dogs. Lawrence et al. (1996b) studied the effect of dexmedetomidine on organ blood flow to determine whether cardiac output reduction is associated with impaired perfusion and oxygenation of vital organs. Dexmedetomidine was administered to anaesthetized dogs and organ blood flow measured using radioactive microspheres (Heymann et al. 1977). Systemic O_2 consumption and plasma lactate concentration were also measured. The results indicated that dexmedetomidine preserved blood flow to the brain, heart, liver and kidneys at the expense of less vital organs, and blood flow through arterio-venous shunts. The microsphere technique only measured hepatic arterial blood flow and so it is possible that total liver blood flow may have decreased through reductions in portal venous flow. Dexmedetomidine decreased the whole body O_2 requirements and blood flow to the vital organs remained above levels associated with hypoperfusion, indicating that cardiac output redistribution

induced by dexmedetomidine does not threaten vital tissue. Pypendop & Verstegen (2000) studied the effects of a medetomidine–midazolam–butorphanol combination on renal cortical, intestinal and muscle microvascular blood flow in isoflurane-anaesthetized dogs using laser Doppler techniques. The anaesthetic conditions of this study were said to mimic clinical practice where high doses of medetomidine (1 mg m^{-2} body surface area, 40 μg kg^{-1} for a 25-kg dog) are used before isoflurane anaesthesia. The combination decreased intestinal and skeletal muscle blood flow, although renal cortical blood flow did not differ from that in dogs anaesthetized with isoflurane alone. The limited data available indicate that the reduction in cardiac output induced by α_2 agonists does not cause hypoperfusion of vital organs in healthy dogs.

Cardiac rhythm

The dysrhythmogenic potential of α_2-agonists is controversial. Xylazine increases the likelihood of dysrhythmias in halothane and isoflurane-anaesthetized dogs (Muir et al. 1975; Tranquilli et al. 1988). Although this has been attributed to α_1-receptor stimulation by xylazine, the contribution of α_1-receptors remains controversial (Day & Muir 1993). It has been suggested that this may have contributed to the relatively high incidence of deaths associated with xylazine use found by Clarke & Hall (1990). However, Lemke et al. (1992) failed to demonstrate a link between arrhythmias in isoflurane-anaesthetized dogs and xylazine and medetomidine. Dexmedetomidine does not decrease the dose of epinephrine required to induce arrhythmias during halothane anaesthesia and there is some evidence for a central antiarrhythmic effect (Savola 1989; Hayashi et al. 1991). This effect is abolished by bilateral vagotomy prompting speculation that it results from vagal enhancement of baroreceptor reflex responses to increased blood pressure (Kamibayashi et al. 1995a). The abolition of dexmedetomidine's antiarrhythmic effect by atropine (Kamibayashi et al. 1995a) suggests that efferent vagal activity to the heart is a critical factor. Vagal stimulation increases the myocardial refractory period and decreases the opportunity for re-entrant arrhythmias to become established (Corr et al. 1986) which are the possible basis for adverse halothane/epinephrine interactions. There is evidence that dexmedetomidine's antiarrhythmic effect is mediated through imidazoline receptors because α_2-antagonists having an imidazoline or imidazole structure inhibited antiarrhythmic effects, while non-imidazoline α_2-antagonists produce insignificant inhibition (Kamibayashi et al. 1995b). High concentrations of imidazoline receptors are found in areas of the brain functionally involved in autonomic nervous control. The precise mechanism of dexmedetomidine's effect on cardiac rhythm is unknown. However, imidazoline receptors are probably involved and effects are associated with vagal stimulation. This provides one reason to avoid the co-administration of antimuscarinic and α_2-agonist drugs. A second reason is based on the adverse consequences of positive chronotropy on myocardial oxygenation (Lemke et al. 1992; Alibhai et al. 1996).

Antinociceptive action of α_2-agonists

Alpha$_2$-agonists have potent antinociceptive action in experimental and clinical studies in animals and human beings (Maze & Tranquilli 1991; Pertovaara 1993). However, α_2-agonist-induced sedation currently limits their use for the provision of analgesia, although used for pre-anaesthetic medication, the antinociceptive action contributes to intraoperative analgesia. Antinociceptive synergism between α_2-agonists and opioids is recognized (Ossipov et al. 1990). The mechanism of α_2-agonist-mediated antinociception is not entirely understood; both supraspinal and spinal sites of action are involved. Radio-ligand studies show high density α_2-binding in the substantia gelatinosa and the intermediolateral cell columns of the spinal cord, and a proportion of α_2-receptors have been located on primary afferent terminals (Unnerstall et al. 1984; Yaksh 1985) suggesting a direct spinal action of α_2-agonists. Both radio-ligand and mRNA studies indicate that spinal α_2-receptors are of the α_{2a}-subtype (Uhlén & Wikberg 1991). However, because of their widespread location, α_2-receptor stimulation could suppress nociceptive signals at various points in pain pathways by: (i) inhibiting neurotransmitter release from the primary afferent fibres to second order neurones; (ii) affecting pre- and post-synaptic modulation of nociceptive signals occurring segmentally in the dorsal horn; (iii) influencing descending modulatory systems from the brainstem; or (iv) altering ascending modulation of nociceptive signals in the diencephalon and limbic areas.

Extensive laboratory animal studies investigating the mechanism of α_2-agonist antinociception is confounded by the effects of sedation on beha-

vioural evaluation of analgesia. Sedation complicates conclusions, particularly those involving supraspinally organized pain-related behaviours upon which some tests, e.g. the formalin test, are based. Hypothermia and reduced skin temperature are an artificial cause of decreased pain sensitivity and may complicate results in thermal tests such as the tail flick latency test (Pertovaara 1993).

Mechanism of action of α_2-agonist analgesia

Systemic administration of dexmedetomidine to rats produced dose-dependent antinociception in spinally and supraspinally organized nocifensive responses, which could be antagonized totally by atipamezole (Pertovaara et al. 1990; Fisher et al. 1991). When dexmedetomidine is injected intrathecally, significantly lower doses produce the same level of antinociception that occurs after systemic administration (Fisher et al. 1991). This supports the hypothesis that α_2-agonists produce analgesia at least in part by a spinal mechanism (Xu et al. 2000). In a study involving rats (Hämäläinen & Pertovaara 1995) medetomidine depressed C fibre-mediated input to the spinal dorsal horn, suggesting that selective inhibition of nociceptive input to the primary afferent terminal occurs pre-synaptically. This has been confirmed in studies with α_2-agonists other than medetomidine (Belcher et al. 1978; Fleetwood-Walker et al. 1985; Sullivan et al. 1992). However, a post-synaptic inhibitory contribution is supported by anatomical evidence (Carlton et al. 1991) and the fact that α_2-receptor activation decreases spontaneous activity in nociceptive dorsal horn neurones (Pertovaara et al. 1991).

The *locus coeruleus* (LC) is recognized as an important site of action for α_2-agonist-induced sedation (Williams et al. 1985) and its role in antinociception has been investigated. Guo et al. (1996) found dexmedetomidine injected into the LC of rats was antinociceptive at doses that did not lead to detectable spinal cord concentrations. The antinociceptive effect was reversed by the spinal administration of α_2-antagonists, suggesting that α_2-receptor stimulation in the LC causes antinociception via α_2-receptor activation in the spinal cord. Previous studies demonstrated that dexmedetomidine inhibits LC neurones. Therefore, it is possible that this inhibition decreases noradrenaline release from LC-spinal cord projections, making subsequent activation of α_2-receptors in the spinal cord unlikely. A neuro-anatomical route through which dexmedetomidine-induced depression of LC activity increases spinal cord norepinephrine concentrations and thereby activates spinal α_2-receptors has been suggested (Guo et al. 1996). These workers have proposed that dexmedetomidine-induced LC suppression causes loss of inhibition of other descending noradrenergic neurones leading to increased spinal cord norepinephrine release and antinociception. The role of the LC in α_2-mediated analgesia is contentious and other studies have found conflicting results (Hämäläinen & Pertovaara 1995).

Neuropathic pain and α_2-agonists

Alpha$_2$-agonists may attenuate or even reverse the allodynia that occurs following nerve ligation and other models of neuropathic pain in rats (Yaksh et al. 1995; Wei & Pertovaara 1997). The mechanism is uncertain, but is thought to involve a spinal α_2-receptor effect, and may relate to possible interactions between α_2-agonists and sympathetic nervous outflow (Yaksh et al. 1995). Neuropathic pain is difficult to manage effectively (Arner & Meyerson 1988; McQuay 1988) and α_2-agonists may have potential in treating opioid-resistant pain.

Studies in dogs and cats

A limited number of studies have investigated the analgesic efficacy of dexmedetomidine and medetomidine in small animal species (Vainio & Ojala 1994; Barnhart et al. 2000; Grimm et al. 2000). Kuusela et al. (2000) compared analgesia following medetomidine, dexmedetomidine and levomedetomidine administration and found dexmedetomidine analgesia (20 μg kg^{-1}) to be slightly longer lasting than that of racemic medetomidine (40 μg kg^{-1}). This suggests that the levo-enantiomer may have some interaction with the dextroform. The analgesic effect of medetomidine in dogs is believed to begin at plasma concentrations of 1–5 ng mL^{-1} (Salonen 1992) although another study (Kuusela et al. 2000) could not demonstrate analgesia (assessed by limb withdrawal to toe pinching) at concentrations of 9.5 ng mL^{-1} (measured approximately 60 minutes after administration of a 40-μg kg^{-1} dose IV). However, limb withdrawal may not be the most reliable way of testing analgesia. Using this analgesiometric technique, analgesia after dexmedetomidine (20 μg kg^{-1}) lasts for about 1 hour. This is important when

dexmedetomidine or medetomidine are used for pre-anaesthetic medication insofar that re-dosing may be necessary after 60 minutes. Extensive analgesiometric studies have been performed in cats and suggest that both the intensity and duration of α_2-agonist analgesia is dose-dependent (Ansah et al. 1998, 2000). Analgesia was assessed by scoring the cat's nociceptive response to inter-digital pad and tail pinch, and tail and skin clamp. The maximum dose of medetomidine tested was high, i.e. 150 μg kg^{-1} IM (Ansah et al. 1998). Although medetomidine had analgesic effects at all doses tested, it was not particularly intense, prompting the authors to suggest that it would only be adequate for minor surgical interventions.

Summary

Alpha$_2$-agonist drugs are popular in small animal practice because their potent sedative and analgesic action contributes to a significant drug sparing effect. Information on cardiovascular safety is unavailable. When medetomidine is administered alone, some cardiovascular effects are maximal at 5 μg kg^{-1} (Pypendop & Verstegen 1998) although higher doses cause more potent coronary artery vasoconstriction, while sedation and analgesia are dose dependent. This suggests that there is little advantage in lower doses (<10 μg kg^{-1}) because analgesia is of shorter duration (<1 hour) drug sparing effects are reduced, while cardiovascular effects are the same. Most anaesthetics have adverse dose-dependent cardiovascular side effects. It is currently unclear whether haemodynamic conditions are improved when pre-anaesthetic medication with α_2-agonists allow the use of reduced concentrations of induction and inhalant agents or whether the effects of α_2-agonist drugs are more detrimental. Dose is an important factor in the provision of analgesia: medetomidine doses of 1–2 μg kg^{-1} may be inadequate for postoperative analgesia (Kuusela et al. 2000) causing predominantly sedation. Low dose continuous infusion techniques may be better for providing constant levels of analgesia. In order to realize the full potential of α_2-agonists in veterinary anaesthesia further research into the dose-related cardiovascular effects are required.

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