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Systemic effects and clinical application of dexmedetomidine

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Abstract

Dexmedetomidine is a most potent α -2 adrenergic selective agonist. It is one of the components of the racemic mixture of two enantiomers of medetomidine. It has a selectivity ratio of 1620/1 (α 2/ α 1), which is 5–10 times higher than that for detomidine (260/1) and xylazine (160/1). Dexmedetomidine produces consistent sedation, anxiolysis and muscle relaxation, which makes it a popular sedative agent in veterinary medicine. In veterinary practice, it is used for premedication and as an adjunct to general anaesthesia in several species. Similar to other alpha-2 agonists it exerts its effect through the action on alpha-2 adrenergic receptors. The sedative and anxiolytic effects of α -2 agonists are mediated by agonism of supraspinal autoreceptors situated in the pons, whereas analgesic effects are mediated by agonism of heteroreceptors located in the dorsal horn of the spinal cord. Dexmedetomidine causes a dose-dependent redistribution of blood flow and preserves blood flow to the most vital organs at the expense of organs like skin and pancreases and this distribution of blood flow is not affected by the type of anaesthesia. The pattern of cardiovascular changes may be affected by the dose used and the type of anaesthetic combined with dexmedetomidine. Most anaesthetic drugs, such as propofol, thiopental, isoflurane and halothane have cardiovascular and respiratory side effects that are dose-dependent. Dexmedetomidine is a good anaesthetic adjuvant for general anaesthesia which reduces intra-operative isoflurane consumption provides analgesic-sparing effect without affecting postoperative recovery profile and improved cardiovascular stability and contributes to the provision of balanced anaesthesia.

Keywords: Dexmedetomidine, α -2 agonists, sedation, respiratory effect and cardiovascular effect

Introduction

The ideal sedative or premedication regimen would provide reliable sedation, anxiolysis, muscle relaxation and analgesia, while the influence on the haemodynamic and pulmonary function would be minimal. In addition, it would be reversible. Alpha-2 adrenoceptor agonists are extensively used in veterinary anaesthesiology since the late sixties with the advent of xylazine and use in cattle and horses (Clarke and Hall, 1969) [17]. Currently, α -2 adrenoceptor agonists are used in domestic and several wild species due to their effects on centrally located α -2 adrenoceptors causing sedation and analgesia. Newer drugs such as romifidine, detomidine and medetomidine with a higher selectivity towards α -2 adrenoceptor were developed and introduced in veterinary practice. Currently, the newest and most selective α -2 adrenoceptors agonist drug used in small animals is dexmedetomidine (Seddighi, 2014) [49]. However, similar to other α -2 adrenoceptor agonists, dexmedetomidine is associated with marked adverse effects of the cardiovascular system, which make unsuitable for administration in younger than 6 months or patient with cardiovascular disease (Ko *et al.*, 2009) [26]. Dexmedetomidine causes biphasic changes in arterial blood pressure (ABP) (Bloor *et al.*, 1992) [12]. Activation of peripheral α -2 adrenoceptors in vascular smooth muscle leads to vasoconstriction and increases systemic vascular resistance (SVR) which causes arterial hypertension and reflex bradycardia (Bloor *et al.*, 1992 and Pypendop and Versteegen, 1998) [12, 42]. Activation of α -2 adrenoceptors in the brain causes sedation and analgesia as well as a decrease in sympathetic outflow in conjunction with augmentation of parasympathetic tone, those results in centrally mediated bradycardia followed by a decrease in arterial blood pressure (ABP) (Ruffolo *et al.*, 1993 and MacMillan *et al.*, 1996) [46, 36]. In small animal practice, anaesthesia is commonly maintained with an inhalant anaesthetic such as isoflurane or sevoflurane. Isoflurane effects hemodynamic homeostasis by decreasing SVR and depressing myocardial function (Brahim and Thut, 1984 and Mutoh *et al.*, 1997) [13, 38]. Thus, hypotension is a common problem associated with the administration of inhalant anaesthetics.

Dexmedetomidine decreases vasodilatation and the subsequent reduction in MAP in isoflurane-anesthetized dogs (Ohata *et al.*, 1999) [40]. Dexmedetomidine is a good anaesthetic adjuvant for general anaesthesia which reduces intra-operative isoflurane consumption, provides analgesic-sparing effect without affecting postoperative recovery profile (Reshma *et al.*, 2016) [44].

Mechanism of action

Alpha-2 agonists exert their effects through the action on alpha-2 adrenergic receptors. Alpha-2 receptors are located pre-synaptically and post-synaptically in neuronal as well as non-neuronal tissues and extrasynaptically in the vasculature. Alpha-2 receptors present on noradrenergic neurons are called "autoreceptors" and those on nonnoradrenergic neurons are called "heteroreceptors" (Burton, 1997) [14]. The sedative and anxiolytic effects of alpha-2 agonists are mediated by agonism of supraspinal-autoreceptors situated in the pons (Locus coeruleus), whereas analgesic effects are mediated by agonism of heteroreceptors located in the dorsal horn of the spinal cord (Burton, 1997) [14].

The mechanism of action of dexmedetomidine is unique and differs from others those currently used as sedative agents, including clonidine. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion and decreased intestinal motility in the gastrointestinal tract. It also decreased contraction of vascular and other smooth muscle, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney, decreased intraocular pressure and decreased insulin release from the pancreas (Merz *et al.*, 1978) [37].

In the rat, dexmedetomidine has been shown to bind to α -2A adrenoceptors on the cell membrane of neurons of locus coeruleus and leads to the opening of inward rectifying potassium channels, resulting in hyperpolarization of the membrane (Chiu *et al.*, 1995) [16]. The neuronal hyperpolarization may be a key element in the mechanism of action of α -2 adrenoceptor agonists from the viewpoint of an anaesthesiologist (Birnbaumer *et al.*, 1990) [10].

Sedative effects

The sedative effects of dexmedetomidine are mediated supraspinally, predominantly via activity within the locus coeruleus of the brainstem, while antinociceptive effects result mainly from activity within the spinal cord at both pre and post-synaptic locations within the dorsal horn. Dexmedetomidine absorbed rapidly resulting in a faster onset of sedation and analgesia. In dog's sedation scores and analgesic effect following dexmedetomidine (10 and 20 μ g/kg IV) and medetomidine (40 μ g/kg IV) did not differ significantly with each other during the first hour after administration. Whereas, from 90 minutes onwards, animals receiving the higher dose of dexmedetomidine had greater sedation scores and analgesic effects when compared to medetomidine.

Dexmedetomidine at the dose rate of 5 mcg/kg intravenously produces moderate to profound sedation, that lasting to up to 30 minutes in canines. The combination of dexmedetomidine and acepromazine (0.05 mg/kg) does not modify the intensity of the sedative effect nor prolongs sedative effects of dexmedetomidine. Profoundly sedated animals will remain

spontaneously in lateral recumbency. The mouth can be opened and the tongue may be manually exposed without difficulty (Alvaides *et al.*, 2008) [5]. In dogs, it appears that a ceiling sedative effect is achieved with a dose of 10 mcg/kg. By increasing the intravenous dose of dexmedetomidine from 10 to 20 mcg/kg can increase the duration but not the intensity of sedation (Kuusela *et al.*, 2000) [28].

Analgesic effects

In comparison to sedative action, alpha-2 agonist, induced analgesia is relatively shorter period (Kuusela *et al.*, 2000) [28]. Analgesic effects of dexmedetomidine (20 mcg/kg/IV) longer than the analgesic effects produced by an equipotent dose of medetomidine (40 mcg/kg/IV) (Kuusela *et al.*, 2000) [28]. Dexmedetomidine has both spinal and supraspinal analgesic actions. There was very close association between opioid and α 2-adrenergic receptors (Unnerstall *et al.*, 1984) and the enhanced antinociceptive actions occur following simultaneous administration of agonists at these sites in the spinal cord (Omote *et al.*, 1991). Lower doses of dexmedetomidine (5-10 mcg/kg in dogs and 10-20 mcg/kg in cats) have been combined with opioid analgesics with the expectation of achieving a synergistic analgesic effect. In cats only the highest dose of dexmedetomidine (40 mcg/kg) showed antinociceptive effects to a thermal stimulus applied to the skin (Slingsby and Taylor, 2008) [51]. The dose required to produce analgesia in cats (40 mcg/kg) is relatively high, that can produce a potential unwanted side effects like excessive cardiopulmonary depression.

Hypothermia

Alpha 2-agonists cause dose-dependent hypothermia (MacDonald *et al.*, 1988) [35] due to depression of noradrenergic receptors in the hypothalamus. A slight decrease in rectal temperature was observed in dogs sedated with dexmedetomidine.

Effect of dexmedetomidine on the different systems on the animal.

Respiratory effect

Both medetomidine and dexmedetomidine reduce the respiratory rate (Lerche and Muir 2004 and Acevedo-Arcique *et al.*, 2014) [32, 1]. Cyanosis reported up to 33% in dogs sedated with medetomidine (Hellebrekers, 1993) [23]. Cyanotic animals show insignificant changes to arterial blood oxygen tension and oxygen saturation more than 95%, however, oxygen tension remains low and venous filling is slow. In addition, after the systemic administration of medetomidine or dexmedetomidine, a response to the increased carbon dioxide tension was decreased in consciousness (Sabbe *et al.*, 1994) [47] and anaesthetised dogs (Lerche and Muir, 2006) [33]. However, they induce minimal effects on arterial oxygen or carbon dioxide partial pressures when administered alone to conscious dogs (Sabbe *et al.*, 1994 and Pypendop and Versteegen, 1998) [47, 42]. The higher doses of dexmedetomidine induce mild metabolic acidosis accompanied by a compensatory increase in arterial bicarbonate concentration (Kuusela *et al.*, 2001) [29]. Bettschart-Wolfensberger, (2005) [9] reported a decrease in respiratory rate throughout the 60 min. the observation period, but no change in arterial PaO₂ or PaCO₂ when dexmedetomidine was administered intravenously in ponies. A transitory decrease in respiratory rate was observed after a single administration of dexmedetomidine in cats (Ansah *et al.*, 1998 and Selmi *et al.*,

2003) [6, 50]. Concurrent administration of dexmedetomidine with butorphanol, midazolam, fentanyl and ketamine resulted in a significant decrease in the respiratory rate in both dogs and cats (Ahmad *et al.*, 2013 and Santosh *et al.*, 2013) [2, 4, 48]. Isoflurane anaesthesia in dogs caused more respiratory depression alone, in compare along with medetomidine or dexmedetomidine (Bloor *et al.*, 1989 and Nguyen *et al.*, 1992) [11, 39]. It is due to a decreased requirement of isoflurane to maintain anaesthesia.

Cardiovascular effect

Dexmedetomidine, similarly to other α -2 adrenoceptor agonists, has marked cardiovascular effects that are mediated by peripheral (Flacke *et al.*, 1990) [20] and central receptors (Link *et al.*, 1996 and MacMillan *et al.*, 1996) [34, 36]. Typically, after a bolus, initial vasoconstriction and increase in SVR occurs, leading to a transient elevation of ABP and CVP and a reduction of HR (Bloor *et al.*, 1992 and Flacke *et al.*, 1993) [12, 21]. It causes a decrease in cardiac output as much as 70% despite persistently elevated blood pressure. The cardiac output reduction affects the blood flow differently among the different organs (Talke *et al.*, 2000 and Pypendop and Versteegen, 2000) [52, 43]. After the administration of dex- or medetomidine, a dose-dependent redistribution of blood flow occurs. Dexmedetomidine preserves blood flow to the most vital organs like brain, heart, liver and kidney, at the expense of organs like skin and pancreases and this distribution of blood flow is not affected by the type of anaesthesia (Lawrence *et al.*, 1996) [30]. The pattern of cardiovascular changes may be affected by the dose used and the type of anaesthetic combined with dexmedetomidine. A direct negative inotropic effect of dexmedetomidine on the myocardium is unlikely to occur (Housmans, 1990 and Flacke *et al.*, 1992) [24, 22]. Coronary blood flow is reduced with doses higher than 1 μ g/kg, while the coronary vascular resistance is increased (Flacke *et al.*, 1993) [21]. In addition, increases in systemic and myocardial oxygen concentrations are indicative of hypoxemia (Flacke *et al.*, 1993) [21]. Roekaerts *et al.* (1996) [45] described non significant changes in the oxygen and lactate concentration despite an increased myocardium vascular resistance and reduce blood flow. These results are similar to those reported by Jalonen *et al.* (1995) [25], who observed no signs of myocardium ischemia in dexmedetomidine-treated pigs. Intracoronary infusion of dexmedetomidine was associated with a reduction of reperfusion-induced arrhythmias in the same species (Yoshitomi *et al.*, 2012) [55].

Endocrine effect

Various studies have reported that α 2-agonists reduce the release of perioperative levels of stress-related hormones and thus attenuate the stress response of surgery in canines (Benson *et al.*, 2000) [8]. In human anaesthesia and surgery, the stress response of surgery is an important factor contributing to patient morbidity, so, pre-anaesthetics like a α 2-agonist can be used to minimize this response (Desborough, 2000) [19].

Gastro-intestinal effect

Alpha-2 agonists decrease the salivation, gastric secretion, gastro-esophageal sphincter pressure, esophageal, gastric and small intestinal motility. Vomiting causes by another α 2-adrenoceptor agonist like xylazine in cats is due to stimulation of receptors in the chemoreceptor trigger zone in the brain

(Colby *et al.*, 1981). Similar effect could have been observed with dexmedetomidine. They may promote ulcer formation. Alpha-2 induces vomiting in 8-20% of canines and up to 90-100% of felines (pypendop, 2005) [41]. Development of aspiration pneumonia may occur with dexmedetomidine, if a properly inflated cuffed endotracheal tube is not in place. Administration of anticholinergic agents 10 to 20 min before administration of alpha-2 agonists, reduce the occurrence of vomiting in canines (Lemke, 2001) [31]. In general, α 2-adrenergic agonists decrease acid gastric and salivary secretions and prolong intestinal transit time. It decreases the motility of the colon dramatically in canines (Asai *et al.*, 1998) [7]. Dexmedetomidine inhibits gastric emptying and gastrointestinal transit in rats (Asai *et al.*, 1998) [7]. Inhibitory effect of morphine on gastrointestinal transit is markedly enhanced by dexmedetomidine, but it did not have significantly effect on gastric emptying.

Clinical use

Dexmedetomidine generally combined with butorphanol for premedication prior to induction of general anaesthesia using propofol. Most anaesthetic drugs, such as propofol, thiopental, isoflurane and halothane have cardiovascular and respiratory side effects that are dose-dependent. Therefore, a reduction in the dose of these agents can lead to improved cardiovascular stability and contributes to the provision of balanced anaesthesia. Kuusela *et al.* (2001) [29] studied various premedicant doses of dexmedetomidine administered intravenously in canines under propofol and isoflurane anaesthesia and found that dose level up to 20 μ g/kg preserved blood pressure but profound bradycardia occurred at the dose 20 μ g/kg. The dose level of 2 μ g/kg resulted in more stable cardiovascular effects but the effect was short period and a stable plane of anaesthesia was difficult to maintain. Dexmedetomidine also decreases the minimum alveolar concentration (MAC) of inhalant anaesthetic for maintaining anaesthesia in a dose-related fashion. In dogs, isoflurane MAC was reduced by 89% after 30 minutes of dexmedetomidine administration (20 μ g/kg/IV) (Bloor *et al.*, 1992) [12]. In dogs receiving dexmedetomidine (5-10 μ g/kg) combined with opioids, the requirements of injectable agents for allowing orotracheal intubation may be markedly decreased. In this case, doses of propofol as low as 0.5 to 1 mg/kg may be enough for placing the orotracheal tube. The administration of inhalant anaesthetic agent during the early phase of maintenance of anaesthesia (30 minutes) becomes less than 0.5%.

Epidural administration of dexmedetomidine in dogs results in a prolonged analgesic effect, with the use of lower doses than those used by intravenous administration (Sabbe *et al.*, 1994) [47]. Dexmedetomidine at the dose rate of 3.0 and 6.0 mcg/kg epidurally in canine caused clinically significant decreases in isoflurane MAC (defined as a reduction in MAC above 20%) for approximately 2 and 4.5 hours, respectively (Campagnol *et al.*, 2007) [15]. Continuous rate infusion (CRI) of dexmedetomidine in healthy dogs is being recommended as an adjunct to general anaesthesia as it reduces the dosage of general anaesthesia, provides a stable plane of anaesthesia and additional analgesia (Uilenreef *et al.*, 2008 and Valtolina *et al.*, 2009 Congdon *et al.*, 2013) [53, 54, 18]. Dexmedetomidine can be used along with diazepam, midazolam, butorphanol, buprenorphine, fentanyl and ketamine, these combinations have been found both effective and safe in healthy dogs (Ahmad *et al.*, 2011 Ahmad *et al.*, 2013 and Santosh *et al.*,

2013) [3, 2, 4, 48]. Dexmedetomidine is also very effective for intra-articular use. Like opioid, alpha-2 adrenoreceptors are distributed throughout the peripheral nervous system. By inhibiting the release of norepinephrine locally, they reduce noxious input and minimize the development of peripheral sensitization. Intraarticular used of dexmedetomidine (1-2.5 µg/kg) with morphine (0.1 mg/kg) and bupivacaine (0.5-1.0 mg/kg) provide long-lasting analgesia for arthrotomy.

Dexmedetomidine can provide postoperative analgesia from 0.5 to 4 hours. However, this duration of analgesia is dependents on a number of others factors. Due to the pronounced cardiovascular effects, dexmedetomidine should only used in clinically healthy dogs and cats (ASA classes I and II). Animals should be frequently monitored for cardiovascular function and body temperature during sedation or anaesthesia. Dexmedetomidine should not be used in patients with pre-existing hypotension, hypoxia or bradycardia. Apnea may occur with dexmedetomidine, therefore in the event of apnea, additional oxygen should be supplied.

Implications and recommendations

The ideal sedative or preanaesthetic agents provide reliable anxiolysis, muscle relaxation, sedation and analgesia with minimal and reversible effects on the hemodynamic and pulmonary function (Kumar *et al.*, 2020) [27]. Dexmedetomidine is a very specific alpha-2 agonist, exerts well-defined effects on different body systems. It preserves the cardiovascular function better than any other alpha-2 agonists, in spite of being more potent. In veterinary practice, it is being used mainly in small animals like dogs and cats. Extensive studies are needed in the future to elucidate its application as clinical anesthesia for ruminants, since ruminants are very sensitive to common alpha-2 agonists like xylazine. It should also be evaluated as an adjunct to different anesthetics and analgesics for general and epidural anesthesia and pain management in bovine and equine species. Being a very potent alpha-2 agonist, dexmedetomidine can be studied, for sedation and capture of wild animal species.

Conclusion

Dexmedetomidine is most potent α -2 adrenergic selective agonist. It produces consistent sedation, anxiolysis and muscle relaxation, which makes it most important sedative agent in veterinary medicine. Dexmedetomidine produces moderate to profound sedation, that lasting up to 30 minutes in canines. Dexmedetomidine preserves blood flow to the most vital organs like brain, heart, liver and kidney, at the expense of organs like skin and pancreases and this distribution of blood flow is not affected by the type of anaesthesia. Dexmedetomidine can be used along with diazepam, midazolam, butorphanol, buprenorphine, fentanyl and ketamine, these combinations have been found both effective and safe in healthy dogs. General anaesthesia like propofol, thiopental, isoflurane and halothane has cardiovascular and respiratory side effects that are dose-dependent. Dexmedetomidine reduce dose of these agents and preserve cardiovascular and respiratory function.

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