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DEXMEDETOMIDINE AND LEVOMEDETOMIDINE, THE ISOMERS OF MEDETOMIDINE, IN DOGS

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ACADEMIC DISSERTATION

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ABSTRACT

The effects of dexmedetomidine as a sedative and premedicant were studied in healthy laboratory beagles. Dexmedetomidine, a potent and selective α_2-adrenoceptor agonist, is the active ingredient of medetomidine, a commonly used sedative in animals.

The clinical effects and pharmacokinetics of medetomidine, dexmedetomidine and levomedetomidine were compared to determine whether dexmedetomidine offers any benefit over racemic medetomidine. A high dose of levomedetomidine was used to evaluate whether it has any pharmacological activity or would influence the sedative and analgesic effects of dexmedetomidine in dogs. Medetomidine and dexmedetomidine were compared as premedicants prior to propofol/isoflurane anaesthesia, and the most appropriate premedicant dose level was determined. Perianaesthetic effects of intramuscular dexmedetomidine were studied, including 24-hour Holter monitoring to detect arrhythmias. The suitability of a cold pressor test as a stress stimulus using dogs sedated and premedicated with dexmedetomidine as a model was evaluated.

Dexmedetomidine was at least as safe and effective as the corresponding dose of medetomidine as a sedative, analgesic and premedicant in laboratory beagles. Levomedetomidine caused no observable behavioural effects in conscious dogs. However, it did reduce the sedative and analgesic effects of dexmedetomidine and intensified bradycardia, suggesting that dexmedetomidine might be preferable instead of medetomidine for use in dogs. The pharmacokinetics of dexmedetomidine and racemic medetomidine were similar, but clearance of levomedetomidine was more rapid than that of the other drugs. A dose of 2 µg/kg of dexmedetomidine resulted in the most stable cardiovascular effects when used as a premedicant before propofol/isoflurane anaesthesia. After dexmedetomidine premedication, propofol/isoflurane anaesthesia was considered more useful than propofol infusion due to a milder degree of respiratory depression and faster recovery. The cold pressor test produced variable responses among the dogs and was not a reliable stress stimulus with the dexmedetomidine dose used. In beagles treated with dexmedetomidine alone or in combination with propofol infusion or propofol/isoflurane, ventricular arrhythmias were detected no more frequently than in healthy non-anaesthetized dogs.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I
Kuusela E, Raekallio M, Anttila M, Falck I, Mölsä S, Vainio O.
Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *J Vet Pharmacol Therap* 2000; 23: 15-20.

II
Kuusela E, Vainio O, Kaistinen A, Kobylin S, Raekallio M.
Sedative, analgesic, and cardiovascular effects of levomedetomidine alone and in combination with dexmedetomidine in dogs. *Am J Vet Res* 2001; 62 (4): 616-621.

III
Kuusela E, Raekallio M, Väisänen M, Mykkänen K, Ropponen H, Vainio O.
Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. *Am J Vet Res* 2001; 62(7): 1073-1080.

IV
Kuusela E, Vainio O, Short CE, Leppäluoto J, Huttunen P, Ström S, Huju V, Valtonen A, Raekallio M.
A comparison of propofol infusion and propofol/isoflurane anaesthesia in dexmedetomidine premedicated dogs. *J Vet Pharmacol Therap* 2003; 26: 1-6.

V
Kuusela E, Raekallio M, Hietanen H, Huttula J, Vainio O.
24-hour Holter-monitoring in the perianaesthetic period in dogs premedicated with dexmedetomidine. *Vet J* 2002; 164: 235-239.

ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
ANOVA	analysis of variance
AV	atrioventricular
cAMP	cyclic adenosine 3′, 5′-monophosphate
cGMP	cyclic guanosine 3′, 5′-monophosphate
CI	confidence interval
CNS	central nervous system
CPT	cold pressor test
GABA	gamma-aminobutyric acid
GDP	guanosine diphoshate
GTP	guanosine triphosphate
im	intramuscular
ip	intraperitoneal
iv	intravenous
MAC	minimal alveolar concentration
p_aCO_2	arterial blood carbon dioxide tension
p_aO_2	arterial blood oxygen tension
sc	subcutaneous
SD	standard deviation
VPC	ventricular premature contraction

1. INTRODUCTION

Medetomidine is a potent and selective α_2-adrenoceptor agonist that contains equal parts of two optical enantiomers, dexmedetomidine and levomedetomidine. Enantiomers are isomers which are mirror images of each other, but in biological systems they may show differences in pharmacological activity and drug distribution in the body.

Medetomidine is used as a sedative, analgesic and anaesthetic premedication in animals, primarily in dogs and cats. It rapidly produces dose-dependent and reliable sedation and analgesia with good muscle relaxation. Potent anaesthetic-sparing effects of medetomidine allow the use of lower doses of anaesthetics as a part of balanced anaesthesia. Perioperative relief of pain and stress is another valuable property of medetomidine. If needed, the effects can be antagonized with a specific antagonist, atipamezole.

Dexmedetomidine, as the active ingredient of the racemic mixture, has gained more interest than the racemate medetomidine in human anaesthesiology. In intensive care patients, dexmedetomidine is used to achieve sedation without respiratory depression, and cardiac patients may benefit from the perioperative cardiovascular stability it induces. Dexmedetomidine has also been studied in dogs, and its clinical effects are presumed to be comparable with those of racemic medetomidine.

2. REVIEW OF THE LITERATURE

2.1 α-adrenergic receptors

Adrenergic receptors α and β mediate the actions of noradrenaline and adrenaline. The α-adrenergic receptors are divided into α_1 and α_2 types according to differential agonist and antagonist affinities. Most α_1-adrenoceptors are located postsynaptically, while α_2-adrenoceptors are found in various neuronal and nonneuronal sites. The activation of α_1-adrenoceptors results in the release of noradrenaline, whereas α_2-adrenoceptor activation inhibits noradrenaline release from sympathetic nerve terminals (Langer, 1981). Both receptors play a significant role in the regulation of vascular tone and arterial blood pressure, but their relative contribution to the balance of vasoconstriction and vasodilatation varies between animal species (Piascik et al., 1996).

2.2 α_2-adrenergic receptors

The α_2-adrenergic receptor is a protein structure that is able to bind to extracellular ligands of endogenous hormones or exogenous drugs. When an agonist binds to a α_2-adrenergic receptor, the structure of the receptor changes, resulting in coupling with G-proteins (guanine nucleotide binding proteins) (Figure 1). Transmembrane signalling is promoted by the replacement of guanosine diphosphate (GDP) with guanosine triphosphate (GTP). Activated receptors inhibit adenylyl cyclase, resulting in a decrease in the accumulation of intracellular cyclic adenosine 3', 5'-monophosphate (cAMP), thus attenuating phosphorylation of target regulatory proteins. Efflux of K^+ through an activated channel causes hyperpolarization, and neuronal firing is suppressed. Ca^{2+} entry into the nerve terminals is also reduced by α_2-adrenoceptor stimulation, which may in turn be responsible for its inhibitory effect on secretion of neurotransmitters (Hayashi & Maze, 1993; Piascik et al., 1996; Khan et al., 1999b).

α_2-adrenergic receptors are divided into the pharmacologically different subtypes α_{2A}, α_{2B} and α_{2C}. In the central nervous system (CNS), α_{2A} is the prevalent subtype, and the major noradrenergic nucleus in the brain stem, locus coeruleus, contains only subtype α_{2A} (MacDonald & Scheinin, 1995). Species differences in distribution of subtypes may exist (Maze & Fujinaga, 2000).

The α_{2A}-adrenoceptor most likely regulates the release of neurotransmitters from noradrenergic neurones (MacDonald & Scheinin, 1995). In genetically modified mouse lines, α_{2A}-adrenoceptor has been shown to be the predominant subtype involved in the mediation of the antinociceptive, sedative, anaesthetic-sparing and hypothermic actions of dexmedetomidine (Hunter et al., 1997; Lakhlani et al., 1997). The α_{2A}-adrenoceptor subtype also appears to have a critical role in the hypotensive response to α_2-adrenoceptor agonists, despite data implicating a role for independent imidazoline binding sites in this response (MacMillan et al., 1996). Moreover, it is considered the primary mediator of α_2-adrenoceptor-mediated spinal analgesia (Stone et al., 1997; Guo et al., 1999), being necessary for analgesic synergy with opioids (Stone et al., 1997).

The α_{2B}-adrenoceptor mediates the major component of the immediate hypertensive action and counteracts the hypotensive action of α_{2A}-receptors. In mice devoid of α_{2B}-receptors, the hypotensive effect occurred immediately and was of greater magnitude than in normal mice, but the bradycardic response was similar (Link et al., 1996).

The α_{2C}-adrenoceptor contributes to spinal analgesia, adrenergic-opioid synergy

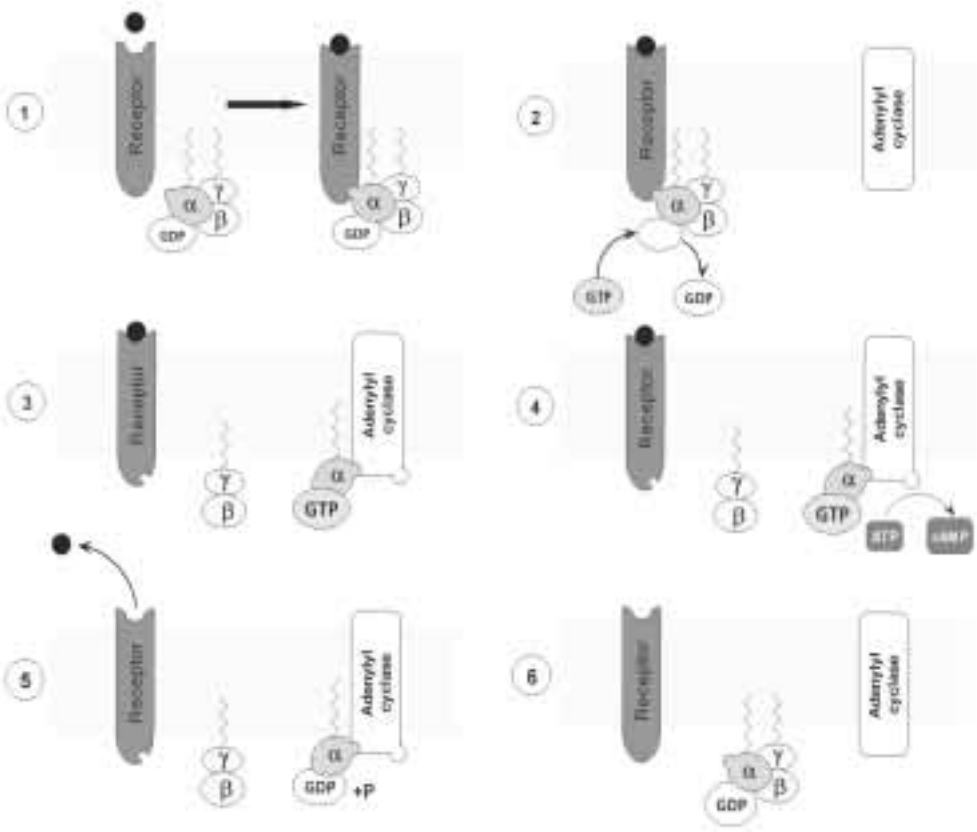

Figure 1
G-protein-coupled receptor and activation of adenylyl cyclase.
1) The adrenergic agonist binds to the receptor, activating binding of the G_S protein; 2) The G_S-protein releases GDP and binds GTP; 3) The G_S-protein splits into $\beta\gamma$ and α_S units, which activates adenylyl cyclase; 4) Production of cyclic AMP (cAMP) is enhanced; 5) GTPase hydrolyses GTP into GDP, releasing α_S from adenylyl cyclase; 6) α_S combines with the $\beta\gamma$ unit to form the G- protein. In the case of α_2-adrenergic agonists, G_i-proteins (instead of G_S above) inactivate adenylyl cyclase.

Modified from http://perth.uwlax.edu/faculty/howard/MCATreview1/sld031.htm

(Fairbanks et al., 2002), hypothermic action and modulation of dopaminergic activity (Sallinen et al., 1997) but seemingly produces no haemodynamic effects (Link et al., 1996). Dexmedetomidine inhibits the release of noradrenaline at the sympathetic innervation of kidney cortex via activation of α_{2C}-adrenoceptors (Taoda et al., 2001).

Subtype-selective drugs suitable for in vivo use are still non-existent (Schwartz & Clark, 1998; Kamibayashi & Maze, 2000), although some evidence of subtype selectivity of dexmedetomidine in vitro has been shown (Jansson et al., 1994; Peltonen et al., 1998).

2.3 Imidazoline receptors

Some effects of α_2-adrenergic agonists may be due to their binding and action in the non-adrenergic imidazoline (imidazole) receptors. The physiological function of imidazoline receptors is controversial, but at least the hypotensive effect of α_2-adrenoceptor agonists may in part be mediated by these receptors in the ventral medulla (Ernsberger et al., 1990; MacDonald & Scheinin, 1995; McCallum et al., 1998). Presumably, they also play a role in the protection against adrenaline-induced arrhythmias (Hayashi et al., 1993; Khan et al., 1999b).

2.4 Dexmedetomidine

Dexmedetomidine, (+) -4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole (Figure 2), is a selective and potent α_2-adrenergic agonist. The α_2/α_1 selectivity of dexmedetomidine is several times higher than that of clonidine, detomidine or xylazine (Virtanen et al., 1988; Aantaa et al., 1993). Dexmedetomidine is therefore considered a full agonist of the α_2-adrenoceptor, and clonidine a partial agonist. More potent sedation and analgesia with minor cardiovascular depression from α_1-adrenoceptor activation can be expected as a result of full agonism.

Dexmedetomidine contains an imidazole in its chemical structure and has an affinity for imidazoline receptors, despite weaker than that for α_2-adrenoceptors (Wikberg et al., 1991; Khan et al., 1999b).

2.4.1 Cardiovascular effects of dexmedetomidine

The cardiovascular effects of dexmedetomidine have been studied extensively in animals and humans but are not yet fully understood. Species-specific differences, particularly between humans and dogs, appear to exist in haemodynamic response to α_2-adrenoceptor agonists (Flacke et al., 1990, 1993; Bloor et al., 1992b; Ebert et al., 2000).

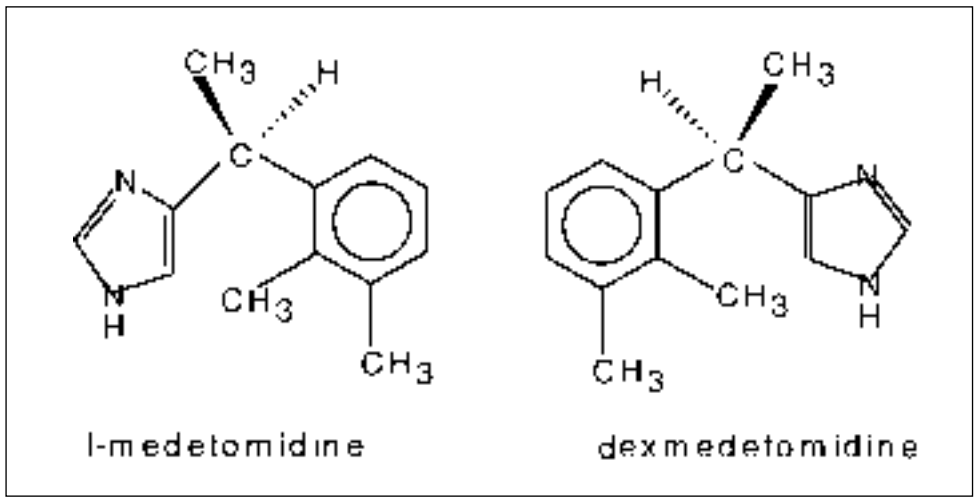

Figure 2
Structure of the medetomidine enantiomers.

Peripheral α-adrenoceptors mediate vascular contraction by regulating calcium influx. After administration of dexmedetomidine, an initial pressor response is produced via vasoconstriction, followed by a secondary baroreflex-mediated decrease in heart rate. Systemic vascular resistance is increased and cardiac output is decreased. Bradycardia is subsequently produced mainly via diminished sympathetic (Schmeling et al., 1991; Xu et al., 1998; Hogue et al., 2002) and/or augmented parasympathetic tone (Bloor et al., 1992b), and blood pressure declines gradually to or beyond baseline level (Bloor et al., 1992a, 1992b). The site of central control of blood pressure is suggested to be the rostral ventrolateral medulla (Hong et al., 1992). Despite later hypotension, heart rate does not increase, which suggests an inhibitory effect on the baroreflex or resetting of the baroreflex (Xu et al., 1998). In humans, baroreflex sensitivity was unaffected while systemic sympathetic tone was reduced by dexmedetomidine (Hogue et al., 2002). Dogs may exhibit a more profound vasoconstrictive response to α_2-adrenoceptor agonists than humans, as indicated by a greater degree of systemic vascular resistance and a lesser degree of subsequent hypotension after dexmedetomidine administration (Flacke et al., 1990; Bloor et al., 1992, 1992b). However, in humans dexmedetomidine doses are much smaller than those commonly used in dogs. In a stepwise infusion study, the highest achieved plasma concentration of dexmedetomidine in human volunteers was 14.7 ± 0.78 ng/ml, resulting in distinct increases in arterial pressures and systemic vascular resistance with decreases in heart rate, stroke volume and cardiac output. At the lower (clinically used) plasma concentrations arterial pressures decreased with less effect on the other cardiovascular parameters (Ebert et al., 2000). Increasing doses of dexmedetomidine (up to 0.6 ng/ml) increased blood pressure in anaesthetized volunteers and decreased it in awake subjects (Talke et al., 2003), showing the effect of baseline sympathetic tone in dexmedetomidine studies. A peripherally active α_2-adrenoceptor antagonist was shown to prevent the immediate pressor effects of dexmedetomidine but to preserve the majority of the late cardiovascular effects in dogs (Pagel et al., 1998b). In addition to species and dosing differences, the magnitude of hypertension is influenced by the administering method of dexmedetomidine. Intramuscular (im) injection generally results in less abrupt changes in blood pressure, and a slow infusion rate may be preferable to a bolus intravenous (iv) administration (Dyck et al., 1993).

Dexmedetomidine has been found to depress cardiac function in dogs even after autonomic denervation (Flacke et al., 1990). Postsynaptic α_2-adrenoceptors are considered nonexistent in the mammalian heart (Dukes & Vaughan Williams, 1984; Hayashi et al., 1991), and dexmedetomidine has shown no direct depressant effect on the canine myocardium (Flacke et al., 1992). Schmeling et al. (1991) interpreted the depression in heart function caused by dexmedetomidine to be the result of increased arterial pressure, but in isolated canine hearts, dexmedetomidine-induced increased afterload did not impair cardiac function (Flacke et al., 1992). In a later study, Flacke et al. (1993) reported diastolic dysfunction and a decline in systolic contractility in conjunction with decreasing catecholamine levels after dexmedetomidine administration. When haemodynamic changes were antagonized by a calcium channel blocker, cardiac function was nevertheless reduced after dexmedetomidine administration in dogs, probably due to sympatholysis (Roekaerts et al., 1997).

The decrease in cardiac output after dexmedetomidine is caused mainly by a decrease in heart rate. While the increase in blood pressure and the decrease in cardiac output occur simultaneously, the latter seems not to be completely mediated reflexly (Flacke et al., 1990). Reduced stroke volume, increased afterload, reduced metabolic demands (Bloor et al.,

1992b; Ebert et al., 2000), low catecholamine levels and coronary vasoconstriction (Flacke et al., 1990; Bloor et al., 1992b) have been suspected to contribute to the reduction in cardiac output. The pressor response to iv dexmedetomidine was enhanced after autonomic denervation (Flacke et al., 1990; Schmeling et al., 1991), but cardiac output decreased without a change in heart rate (Flacke et al., 1990). Likewise, when bradycardia was blocked by glycopyrrolate pretreatment, the decrease in cardiac output was only partially reversed, but arterial pressure increased further (Bloor et al., 1992b). Iv dexmedetomidine (Lawrence et al.,1996a) and im medetomidine (Pypendop & Verstegen, 2000) have been shown to considerably redistribute cardiac output in dogs, reducing blood flow to less vital organs and preserving it in vital organs to levels above those known to induce underperfusion.

Iv dexmedetomidine has been shown to induce coronary vasoconstriction in dogs (Schmeling et al., 1991; Flacke et al., 1993). However, in canine myocardial ischaemia models, iv dexmedetomidine preserved endocardial perfusion and decreased myocardial oxygen demand, thereby reducing oxygen deficiency of the ischaemic myocardium (Lawrence et al., 1996b; Roekaerts et al., 1996; Willigers et al., 2003). In pigs, large iv doses of dexmedetomidine caused moderate regional coronary vasoconstriction without metabolic signs of myocardial ischaemia (Jalonen et al., 1995). In goats, the cardiovascular response to iv dexmedetomidine was found to be similar to that of man; systemic and coronary vasoconstriction was short-lived, and the balance between myocardial oxygen supply and demand was maintained (Lawrence et al., 1997).

2.4.1.1 Cardiovascular effects of dexmedetomidine in humans

Blood pressure was reduced after iv dexmedetomidine (≤1 µg/kg) by 10% to 20% and heart rate usually decreased moderately (Kallio et al., 1989; Aantaa et al., 1990a, 1990b; Aantaa 1991a; Jaakola et al., 1991; Jaakola, 1994). Iv dexmedetomidine (0.25 to 2.0 µg/kg) produced a transient increase in blood pressure and a longer lasting decrease in blood pressure, heart rate and cardiac output (Bloor et al., 1992a).

Im administration of dexmedetomidine (2 µg/kg) avoided the acute haemodynamic changes seen with iv administration but led to similar haemodynamics within four hours (Dyck et al., 1993). Preoperative im dexmedetomidine (<1.5 µg/kg) resulted in a lower heart rate and blood pressure than placebo during thiopentone anaesthesia (Aantaa 1991b). Im dexmedetomidine (1.5 µg/kg) decreased blood pressure 22% and heart rate by 32% in healthy volunteers, with no signs of initial increase in blood pressure. The hypotension was still present after six hours when all signs of sedation had disappeared (Scheinin H et al., 1992). In elderly patients, im dexmedetomidine (1 µg/kg) induced a moderate decrease in blood pressure and a slight decrease in heart rate (Virkkilä et al., 1994).

Infusion of dexmedetomidine (0.2 or 0.6 µg/kg/h) into healthy volunteers resulted in minor changes in cardiovascular parameters (Hall et al., 2000), and postoperative increases in heart rate and blood pressure were attenuated without significant bradycardia or hypotension (Talke et al., 1997). Increasing concentrations of dexmedetomidine (from 0.7 to 14.7 ng/ml) resulted in progressive decreases in heart rate and cardiac output, with a maximal decrease in heart rate of 29% (Ebert et al., 2000). In one case, intraoperative infusion of dexmedetomidine (0.3 µg/kg/h) resolved tachycardia, which had been unresponsive to beta-adrenergic blocker therapy (Ruesch & Levy, 2002).

ECG abnormalities related to dexmedetomidine other than sinus bradycardia have been rarely reported in humans. After iv dexmedetomidine was administered to 28 healthy

males, one event of a R-R interval lasting 2.4 seconds and two episodes of junctional escape rhythm were detected (Bloor et al., 1992a). A sinus arrest and a symptomatic bradycardia resulting in loss of consciousness were detected in one out of 15 patients receiving iv dexmedetomidine, but atropine normalized the heart rate (Jaakola, 1994). One patient out of 22 receiving dexmedetomidine infusion at plasma concentration of 0.32-0.35 ng/ml had a long sinus pause during intubation (Talke et al., 2000).

2.4.1.2 Cardiovascular effects of dexmedetomidine in dogs

In conscious dogs iv dexmedetomidine 1.25 µg/kg increased arterial pressure by 15% and decreased heart rate by 26% and cardiac output by 35% (Schmeling et al., 1991). Under isoflurane anaesthesia iv dexmedetomidine 20 µg/kg increased arterial pressure by 67%, concomitantly decreasing heart rate by 53% and cardiac output by 74%. Arterial blood pressure remained at least 20% above baseline (under anaesthesia), while heart rate was 40% lower than baseline throughout the four-hour study (Bloor et al., 1992b). Iv dexmedetomidine 10 µg/kg reduced cardiac output by 50% in anaesthetized dogs. Blood flow through skin decreased by 70% to 90% and renal flow by 30%, but cerebral and cardiac blood flows were less affected. Arterial lactate concentrations were unchanged after dexmedetomidine, implying overall adequacy of oxygen supply to the body (Lawrence et al., 1996a). In dogs premedicated with fentanyl, iv dexmedetomidine 10 µg/kg decreased heart rate by 39%, cardiac output by 64% and heart contractility by 29% and increased mean arterial pressure by 55% as compared with baseline (Roekaerts et al., 1997).

Iv dexmedetomidine induced greater reductions in cardiac output in dogs with dilated cardiomyopathy compared with healthy dogs (Pagel et al., 1998a).

The cardiovascular effects of iv racemic medetomidine were fully established with doses as low as 5 µ/kg, and increasing the dose prolonged the effects (Pypendop & Verstegen, 1998). Lombard et al. (1989) studied the effects of im medetomidine in dogs with compensated mitral regurgitation and considered the drug to be safe but recommended the use of an antagonist to reverse cardiovascular effects. The use of anticholinergic drugs aiming to reduce the bradycardia caused by medetomidine is usually not advised, as it may result in prolonged, severe hypertension leading to increased myocardial oxygen demand (Vainio & Palmu, 1989; Short, 1991; Alibhai et al., 1996).

Besides bradycardia, accentuated sinus arrhythmia and sinoatrial and atrioventricular (AV) heart blocks are the most commonly described arrhythmogenic effects of α_2-adrenergic agonist drugs in dogs. AV-blocks (first and second degree) develop as disturbances in the conductivity of the cardiac excitatory impulse. The appearance of AV-blocks after dexmedetomidine administration has not been reported. Iv and im medetomidine has been shown to induce occasional second-degree AV-blocks in dogs (Lombard et al., 1989; Vainio & Palmu, 1989; Ewing et al., 1993; Kramer et al., 1996).

Infusion of dexmedetomidine 0.5 µg/kg/min has been demonstrated to prevent adrenaline-induced arrhythmias in halothane-anaesthetized dogs in a dose-dependent manner. The effect appeared to be mediated at least in part by stimulation of central α_2-adrenoceptors and to be independent of changes in haemodynamic parameters (Hayashi et al., 1991). In a later study, however, the same authors describe imidazoline-preferring receptors rather than the α_2-adrenergic receptor as being responsible for the anti-arrhythmic property of dexmedetomidine. Activation of the imidazoline-preferring receptors presumably increases vagal tone, which may protect against adrenaline-induced arrhythmias (Hayashi et al., 1993). In vagotomized or atropine-treated animals, the anti-arrhythmic effect of dexmedetomidine is abolished (Kamibayashi et al., 1995a). The site of the anti-

arrhythmic action may be the nucleus reticularis lateralis in the ventrolateral medulla, which is rich in imidazoline receptors and functionally connected to the area that modulates vagal activity (Kamibayashi et al., 1995b).

2.4.2 Respiratory effects of dexmedetomidine

The ventilatory effect of dexmedetomidine in humans resembles that of normal non-REM sleep, and its impact on central breathing control seems to be minor (Belleville et al., 1992). Similarly, in dogs, respiratory depression and the effect on hypoxic reflexes caused by dexmedetomidine are relatively mild, but species-specific variations may exist (Nguyen et al., 1992). In rabbits, iv dexmedetomidine produced hypercarbia and hypoxia (Zornow, 1991). In sheep, marked hypoxia may develop after iv and im medetomidine or dexmedetomidine (Raekallio et al., 1998; Kästner et al., 2001a; Kästner et al. 2001b), probably due to pulmonary venospasm-induced alveolar oedema (Bacon et al., 1998).

2.4.2.1 Respiratory effects of dexmedetomidine in humans

In healthy humans breathing room air, iv dexmedetomidine (≤2.0 µg/kg) caused a mild increase in resting arterial blood carbon dioxide tension (p_aCO_2) and a decrease in minute ventilation with little change in respiratory rate, and arterial blood oxygen tension (p_aO_2) remained unchanged. Oxygen consumption increased transiently and then decreased. (Belleville et al., 1992). Partial respiratory obstruction after iv dexmedetomidine (2 µg/kg) was observed in some patients (Lawrence & DeLange, 1997). Arterial oxygen saturation was normal after iv and im dexmedetomidine (Jaakola et al., 1991; Jaakola 1994; Bührer et al., 1994; Talke et al., 1995; Venn et al., 1999). Infusion of dexmedetomidine into healthy volunteers or surgical patients requiring intensive care resulted in minor respiratory changes, which were not considered to be clinically significant (Hall et al., 2000; Venn et al., 2000). The mild respiratory depression observed was deemed to be secondary to profound sedation (Ebert et al., 2000).

2.4.2.2 Respiratory effects of dexmedetomidine in dogs

After administration of dexmedetomidine or medetomidine iv or im, respiratory rate usually decreases with minimal effects on blood gas values (Vainio 1989; Schmeling et al., 1991; Venugopalan et al., 1994; Kramer et al., 1996). Nguyen et al. (1992) found that at low iv dexmedetomidine doses ventilation decreased, but at doses exceeding 20 µg/kg end-tidal CO_2 decreased and end-tidal O_2 increased as compared with awake control values. The authors suggested that this effect might be partially related to the central α_1-adrenoceptor agonist. However, iv dexmedetomidine has been shown to dose-dependently reduce the response to hypercapnia (Nguyen et al., 1992; Sabbe et al., 1994). On the other hand, a combination of iv dexmedetomidine (Nguyen et al., 1992) or medetomidine infusion (Bloor et al., 1989) and isoflurane resulted in less respiratory depression than with isoflurane alone at the same anaesthesia level.

2.4.3 Sedative/hypnotic and MAC-sparing effects of dexmedetomidine

Several reasons exist for dexmedetomidine being advocated as a sedative agent in human medicine. It has a relatively short half-life, which enables the use of a continuous infusion. Sedation and anxiolysis are accompanied by analgesic properties, and under suitable dos-

ing, the patients are readily roused. Minor respiratory effects, stabilizing cardiovascular effects and the availability of a specific antagonist are additional advantages (Hall et al., 2000).

The site of the sedative/hypnotic action of dexmedetomidine resides in the brain stem, in the locus coeruleus, which controls vigilance and modulates sympathetic outflow (Correa-Sales et al., 1992a). In rats depleted of catecholamine stores, intraperitoneal (ip) dexmedetomidine still reduced the minimal alveolar concentration (MAC) of halothane (Segal et al., 1988); thus sympatholysis alone does not explain the MAC-sparing effect of dexmedetomidine. The hypnotic action is mediated by inhibition of adenylate cyclase, which alters phosphoryrylation of the potassium channel (Correa-Sales et al., 1992b). Dexmedetomidine has shown strong synergistic interactions with gamma-aminobutyric acid (GABA)-acting compounds, such as midazolam (Salonen et al., 1992), and has been suggested to partly exert its hypnotic action via GABAergic pathways (Seidel et al., 1995). It may also be associated with a decrease in serotoninergic neurotransmission and was demonstrated to be diminished by serotoninergic stimulation in rats (Rabin et al., 1996a). Decreased glutamatergic neurotransmission, secondary to reduced availability of glutamine has recently been reported to be involved both in sedative/hypnotic- and anaesthetic-sparing effects of dexmedetomidine (Huang & Hertz, 2000). The nitric oxide/cGMP pathway, a major signalling transduction pathway implicated in mechanisms mediating consciousness and pain, seems to be an important mediator of the anaesthetic action of dexmedetomidine (Vulliemoz et al., 1996; Tonner et al., 1999). When halothane and dexmedetomidine were given simultaneously to mice, the decrease in cerebellar cGMP was greater than with either of the drugs alone (Vulliemoz, 1998). Buttermann et al. (1998) suggested that dexmedetomidine produces its anaesthetic effects through different neuroanatomic pathways than volatile anaesthetics. In a study made with tadpoles, dexmedetomidine did not adhere to the Meyer-Overton rule (correlation of lipid solubility with the anaesthetic potency), implicating a more specific site of action than general anaesthetics. However, the anaesthetic action of dexmedetomidine was diminished by increased pressures, demonstrating a similar effect compared with other general anaesthetics, such as barbiturates or propofol (Tonner et al., 1997).

Dexmedetomidine has been shown to bind to and activate α_1-adrenoceptors. Central α_1-adrenoceptor stimulation has been reported to functionally antagonize the hypnotic response to dexmedetomidine by either a specific or a non-specific interaction between the receptors (Doze et al., 1989b; Guo et al., 1991; Schwinn et al., 1991) outside of the locus coeruleus (Correa-Sales et al., 1992a). The transmembrane components involved in the signal transduction mechanism are different for α_1- and α_2-adrenoceptors, but these mechanisms may interact. Pharmacokinetic interaction was considered unlikely, as only a centrally active α_1-adrenoceptor agonist reduced the hypnotic effect of dexmedetomidine (Guo et al., 1991).

Chronic treatment with tricyclic antidepressant desipramine desensitized rats to the hypnotic, analgesic, and MAC-reducing properties of dexmedetomidine. Desipramine was suggested to up-regulate α_1-adrenoceptors, causing hyper-responsiveness and thus inducing the normally weak α_1-adrenoceptor activity of dexmedetomidine to antagonize its α_2-adrenoceptor-mediated effects. The most vulnerable was the response with the least efficacy (hypnosis) (Guo et al., 1998). Only 4% of α_2-adrenoceptors are required for the central noradrenaline turnover suppressant effect of dexmedetomidine, while MAC-reducing action requires >20%, antinociceptive effect >40% and hypnotic effect >80% of the available α_2-adrenoceptors (Hayashi et al., 1995; Rabin et al., 1996b; Guo et al., 1998).

Tolerance does not develop for either the sympatholytic or MAC-sparing action of dexmedetomidine after chronic administration, although it does occur for the hypnotic response (Reid et al., 1994; Rabin et al., 1996b). The most efficient responses have a built-in reserve that sustains the response even when the transduction mechanism is disrupted (Rabin et al., 1996b). Thus, the analgesic properties of dexmedetomidine can persist after the hypnotic response has been attenuated by chronic administration, and animals tolerant of the hypnotic and analgesic actions of dexmedetomidine are still capable of exhibiting MAC-sparing action (Hayashi et al., 1995b). The transduction pathway for analgesia may be more efficiently coupled than that for hypnotic action. Drugs with high intrinsic efficacy require fewer receptors to exert a pharmacological action; clonidine needs 30% more receptors for the analgesic effect than dexmedetomidine, and thus, dexmedetomidine is less susceptible to the development of tolerance (Hayashi et al., 1995a).

In rats, dexmedetomidine caused a slow-frequency, low-amplitude EEG, similar to that seen in slow-wave sleep. Sleep was disturbed after dexmedetomidine sedation, followed by increased wakefulness, representing a down-regulation of α_2-adrenoceptors or a disruption in the mechanism that regulates sleep. Imidazoline receptors may also play a role in the sleep-regulating action of dexmedetomidine (Seidel et al., 1995).

2.4.3.1 Sedative effects of dexmedetomidine in humans

Dose-dependent sedation was observed at iv doses of 0.5 and 1.0 µg/kg (Aantaa 1991a), and significant sedation lasted for three hours after a dose of 2.0 µg/kg (Belleville et al., 1992). Im dexmedetomidine 2.4 µg/kg induced significant sedation and anxiolysis, but patients were responsive (Aho et al., 1992b). Most subjects fell asleep after 1.5 µg/kg im dexmedetomidine but were easily roused, and no signs of sedation were seen after six hours (Scheinin H et al., 1992).

During infusion of dexmedetomidine (<0.6 µg/kg/h) volunteers could be easily roused with verbal or physical stimuli (Hall et al., 2000). At a plasma dexmedetomidine concentration of 0.5 ng/ml, patients were heavily sedated and some of them were only roused by painful stimulation (Bührer et al., 1994). Plasma dexmedetomidine concentration from 1.9 to 14.7 ng/ml produced deep sedation with memory impairment, and at the higher concentrations the volunteers were unresponsive to loud verbal stimuli and shaking (Ebert et al., 2000). In patients requiring intensive care, dexmedetomidine (<0.7 µg/kg/h) was considered a useful agent for the provision of postoperative analgesia and sedation and for reducing morphine requirements (Venn et al., 1999; Triltsch et al., 2002). The patients were easily and calmly roused from sleep to allow communication and co-operation while intubated and ventilated, and then quickly returned to sleep (Venn et al., 1999). Haemodynamic stability was better maintained in intensive care patients receiving dexmedetomidine infusion than in those receiving propofol for sedation (Venn et al., 2001; Triltsch et al., 2002). Interleukin 6 concentration decreased in patients receiving dexmedetomidine infusion, suggesting a beneficial effect on the inflammatory response to surgical trauma (Venn et al., 2001).

2.4.3.2 Sedative effects of dexmedetomidine in animals

Dexmedetomidine has usually been studied in anaesthetized dogs, and the sedative effects of dexmedetomidine in conscious dogs are rarely reported. Iv dexmedetomidine (1 to10 µg/kg) has resulted in dose-dependent sedation in dogs (Sabbe et al., 1994). Racemic im medetomidine has been shown to produce dose-dependent sedation in dogs at doses up to 80 mg/kg (Vainio, 1989). The duration of sedation with medetomidine is dependent on

the dose and route of administration (Vainio, 1989; England & Clarke, 1989; Kramer et al., 1996). In experimental dogs, sedation was observed even at a dose of 1 µg/kg of iv medetomidine (Pypendop & Verstegen, 1998). As with other sedatives, a quiet atmosphere after medetomidine administration is required to maximize the drug's effects (Kramer et al., 1996).

Rats were reported to be dose-dependently sedated at subcutaneous (sc) dexmedetomidine doses of 30 to 300 µg/kg (MacDonald et al., 1991), but at 1000 µg/kg (ip or sc) the level of sedation decreased and evidence of excitation was observed (Doze et al., 1989a; MacDonald et al., 1991; Savola & Virtanen, 1991). Prazosin (an α_1-antagonist) blocked this reversal of sedation. Sc dexmedetomidine 10 mg/kg was a toxic dose to rats causing pulmonary oedema (MacDonald et al., 1991).

2.4.4 Analgesic effects of dexmedetomidine

While the sedative action of dexmedetomidine is mediated at a supraspinal level, the analgesic response is mainly mediated spinally (Hayashi et al., 1995b). A direct action on the locus coeruleus may also be implicated, resulting in activation of α_2-adrenoceptors in the spinal cord through which the antinociceptive effect is mediated (Guo et al., 1996). Pertovaara et al. (1991) suggested that at low doses of medetomidine a supraspinal mechanism is involved, and at higher doses antinociception is more spinally mediated.

The direct spinal component of analgesia induced by dexmedetomidine has been studied in isolated rat spinal cords (Kendig et al., 1991; Savola et al., 1991b). Dexmedetomidine acted in the dorsal horn of the spinal cord by interrupting the nociceptive pathway to the ventral root, thus reducing the spinal reflex. Dexmedetomidine showed a longer linear dose-response relationship than clonidine, which was less effective at higher concentrations. The difference was suggested to be due to the partial agonism of clonidine at the α_2-adrenoceptor or α_1-adrenoceptor-mediated antagonism at higher concentrations (Kendig et al., 1991). Both dexmedetomidine and isoflurane have been shown to suppress nociceptive neurotransmission in the rat spinal cord, without significant interaction between these drugs (Savola et al., 1991b).

Some peripheral antinociceptive effect of dexmedetomidine has been reported, and it may be mediated predominantly by a α_1-adrenoceptor (Idänpään-Heikkilä et al., 1994). The peripheral analgesic action of dexmedetomidine was enhanced after nerve injury (Poree et al., 1998).

2.4.4.1 Analgesic effects of dexmedetomidine in humans

Postoperatively administered iv dexmedetomidine relieved visceral pain and reduced opioid requirement but was attended by sedation and bradycardia (Aho et al., 1991b). Unexpectedly, in one study, patients treated with preoperative im dexmedetomidine experienced more pain than those patients treated with placebo (Aantaa et al., 1991b). Iv dexmedetomidine showed an analgesic effect on ischaemic pain comparable with that of fentanyl, but pain threshold (measured by dental dolorimetry) remained unaffected (Jaakola et al., 1991). Pain threshold to electric stimulation of the tooth pulp and to cutaneous heat were not influenced by a low dose of iv racemic medetomidine, however the unpleasantness of ischaemic pain was reduced (Kauppila et al., 1991). While preoperative iv dexmedetomidine decreased opioid requirements during hand surgery under regional anaesthesia, it had no impact on pain sensation during tourniquet inflation (Jaakola, 1994). Infusion of dexmedetomidine into volunteers decreased pain sensation and blood pressure

response to the cold pressor test (Ebert et al., 2000; Hall et al., 2000) and prevented noradrenaline increase, without influencing adrenaline response (Ebert et al., 2000). Intraoperative dexmedetomidine infusion (0.4-0.7 µg/kg/h) resulted in lower postoperative pain scores and lower opioid requirements than propofol infusion (Arain & Ebert, 2002).

2.4.4.2 Analgesic effects of dexmedetomidine in animals

The analgesic effect of iv dexmedetomidine in dogs has been studied by a thermally evoked skin twitch response and by toe-web pinching (Sabbe et al., 1994), and in anaesthetized dogs by a tail-clamp method (Vickery et al., 1988; Bloor et al., 1992b; Nguyen et al., 1992; Salmenperä et al., 1994). The effect of medetomidine, in contrast has been examined by toe-web pinching (Clarke & England, 1989; England & Clarke, 1989; Hamlin & Bednarski, 1989; Venugopalan et al., 1998; Vainio, 1991), constant current stimulus (Vainio et al., 1989) and skin needle-prick (Ko et al., 1996). Intrathecal, epidural and iv administration of dexmedetomidine has been shown to produce an antinociceptive effect in dogs. After intrathecal and epidural injection, a preferential reduction occurred in the response to pinching of hind paws as compared with forepaws. The spinal effect was unaccompanied by effects on behavioural alertness, motor function or changes in hypercapnic response (Sabbe et al., 1994). Muir et al. (1999) observed no analgesic effect at im medetomidine doses of 2 and 5 µg/kg in dogs of various breeds. In beagles, im medetomidine 10 µg/kg alleviated post-thoracotomy pain better than buprenorphine (Vainio & Ojala, 1994). In canine ovariohysterectomy, im medetomidine 40 µg/kg administered preoperatively provided postoperative analgesia for up to 90 minutes after extubation (Ko et al., 2000).

In rats, the analgesic effect of dexmedetomidine has usually been measured by a spinal reflex causing withdrawal of the paw or tail. Thermal nociception has been studied by a hot-plate test (lick of the paw or a jump) (Idänpään-Heikkilä et al., 1994), a tail-flick test (Kalso et al., 1991; Hayashi et al., 1995a; Guo et al., 1996) and a thermoelectric Peltier device (Poree et al., 1998). Mechanical nociception has been evaluated by a paw pressure test (Idänpään-Heikkilä et al., 1994) and von Frey fibres (Poree et al., 1998). According to De Kock & Meert (1997), stress-induced analgesia may influence the antinociceptive action of dexmedetomidine in rats, and thus housing and handling conditions of animals during testing may affect the study outcome. Intrathecal administration of dexmedetomidine was 7 to 10 times more potent than sc administration in rats, and the antinociceptive effect (six hours) outlasted the sedative effect (Kalso et al., 1991).

In cats, toe-web-, skin-, tail-pinching (Ansah et al., 1998; Ansah et al., 2000) and tail-clamp (Farber et al., 1997; Schmeling et al., 1999) methods have been used to measure the analgesic effect of dexmedetomidine. In cats, raising the blood concentration of dexmedetomidine or medetomidine above a certain level decreased the level of sedation while increasing the level of analgesia (Ansah et al., 2000).

2.4.5 Dexmedetomidine as a premedicant

While usefulness of dexmedetomidine as an anaesthetic adjunct has been extensively studied in humans, regulatory authorities have not yet approved it as a premedicant for humans. Improved cardiovascular stability and the decrease in noradrenaline levels and anaesthetic requirements are considered the most important beneficial effects of dexmedetomidine during anaesthesia. The sympatholytic effect (bradycardia and hypotension) may be excessive in humans (Scheinin H et al., 1993; Talke et al., 1995; Lawrence & DeLange, 1997). Perioperative oxygen consumption has been shown to effectively decrease

after dexmedetomidine (Taittonen et al, 1997). Its effect on perioperative myocardial ischaemia prevention has been evaluated in vascular surgery patients, but patient numbers have been too low to show statistical significance (Talke et al., 1995; Jalonen et al., 1997). While haemodynamic responses to stressful stimuli are blunted by dexmedetomidine, it may reduce the sensitivity of these variables as signs of anaesthetic depth (Erkola et al., 1994).

Dexmedetomidine reduces thiopental distribution and clearance, most probably by decreasing cardiac output with no pharmacodynamic interaction between thiopental and dexmedetomidine (Bührer et al., 1994). This is in contrast with the MAC-reducing effect of dexmedetomidine with volatile agents (a pharmacodynamic interaction) (Vickery et al., 1988; Aho et al., 1991a).

Dexmedetomidine reduces cerebral blood flow without evidence of global cerebral ischaemia (Zornow et al., 1990). It is considered to be a potent neuroprotector (Maier et al., 1993) and has been shown to prevent neonatal ischaemic brain damage in mice (Laudenbach et al., 2002). It also reduces intra-ocular pressure in human cataract surgery patients (Jaakola et al., 1992; Virkkilä et al., 1994).

2.4.5.1 Dexmedetomidine as a premedicant in humans

The optimal iv premedication dose of dexmedetomidine in humans has been reported to be in the range of 0.33-0.67 µg/kg (Aantaa et al., 1990a), but higher (2 µg/kg) doses have also been used (Lawrence & DeLange, 1997). The usual im dexmedetomidine premedication dose has been 2.5 µg/kg (Scheinin H et al, 1993; Levänen et al., 1995; Erkola et al., 1994; Jaakola et al., 1994; Taittonen et al., 1997). Dexmedetomidine premedication has been shown to reduce thiopental (Aantaa et al., 1990a; Aantaa et al., 1990b; Jaakola et al., 1992; Scheinin B et al., 1992), isoflurane (Aho et al., 1991a; Jaakola et al., 1992; Erkola et al., 1994; Lawrence & DeLange, 1997) and opioid (Aho et al., 1991b; Jaakola et al., 1992; Scheinin B et al., 1992; Scheinin H et al., 1992, 1993; Jaakola et al., 1994; Lawrence & DeLange, 1997) requirements. Dexmedetomidine decreased the need for intraoperative ketamine and postanaesthetic delirium effects of ketamine, when compared with midazolam (Levänen et al., 1995). Reduced cardiovascular responses to tracheal intubation (Aho et al., 1991a; Aho et al., 1992b; Scheinin B et al., 1992; Scheinin H et al., 1993; Lawrence & DeLange, 1997) and lower catecholamine concentrations (Scheinin B et al., 1992; Scheinin H et al., 1992; Lawrence & DeLange, 1997) have been reported after dexmedetomidine. Recovery after isoflurane anaesthesia has been faster (Jaakola et al., 1992) or similar (Lawrence & DeLange, 1997) when iv dexmedetomidine was compared with placebo and similar when compared with midazolam-fentanyl (Jaakola et al., 1994). The haemodynamic and sedative effects lasted at least four hours after im injection of the drug, which was considered longer than optimal in connection with minor surgery (Aantaa et al., 1991b).

Intraoperative infusion of dexmedetomidine with a target plasma concentration of 0.6 ng/ml to 0.75 ng/ml has been shown to reduce isoflurane requirement by 47% to 90% (Aho et al., 1992a; Aantaa et al., 1997; Khan et al., 1999a). In vascular surgery patients, it decreased sympathetic tone and attenuated hyperdynamic responses to anaesthesia and surgery but increased the propensity towards hypotension. The requirements of fentanyl, enflurane and beta-blockers and the incidence of fentanyl-induced muscle rigidity and postoperative shivering were decreased in patients receiving intraoperative dexmedetomidine infusion (Jalonen et al., 1997).

Perioperative infusion of dexmedetomidine appeared to benefit haemodynamic man-

agement of vascular surgical patients with less frequent episodes of tachycardia and myocardial ischaemia in the dexmedetomidine group (Talke et al., 1995), and stress responses during emergence of anaesthesia were attenuated (Talke et al., 2000). Sedation was no longer observable the day after surgery despite the infusion of dexmedetomidine continuing, probably due to the desensitizing effects of chronic administration of dexmedetomidine (Talke et al., 1995).

2.4.5.2 Dexmedetomidine as a premedicant in animals

In dogs, iv dexmedetomidine 10 µg/kg decreased the MAC of halothane by more than 90%. There was no response to tail-clamping for more than 1 hour despite halothane was discontinued (Vickery et al., 1988; Vickery & Maze, 1989). Iv dexmedetomidine 20 µg/kg decreased the MAC of isoflurane by 89%. The isoflurane requirement was still 50% reduced at four hours after administration of dexmedetomidine (Bloor et al., 1992b). A low dose of 3 µg/kg of iv dexmedetomidine reduced isoflurane MAC by 70% (Nguyen et al., 1992). In dogs under enflurane anaesthesia, iv dexmedetomidine and fentanyl showed an additive or synergistic interaction with respect to MAC-sparing effect, but the presence of fentanyl increased the degree of bradycardia induced by dexmedetomidine (Salmenperä et al., 1994). Oral dexmedetomidine premedication has also been studied in dogs (Proctor et al., 1991, 1992; Kersten et al., 1993).

Räihä et al. (1989) suggested that the most suitable im premedicant dose of racemic medetomidine in dogs is between 10 and 40 µg/kg, as the lower dose produced inconsistent sedation, and the higher dose excessive sedation. In a clinical study in dogs of various breeds, an im dose of 20 µg/kg of medetomidine (corresponding to 10 µg/kg of dexmedetomidine) was suggested to be optimal for premedication (Young et al., 1990).

In rats, halothane could be discontinued for up to 30 min with no response to tail-clamping after ip dexmedetomidine 100 µg/kg (Segal et al., 1988), and the same dose reduced isoflurane MAC by approximately 90% (Savola et al., 1991a). Schmeling et al. (1999) found that in cats receiving dexmedetomidine lower brainstem or spinal determinants of anaesthetic depth (movement and haemodynamic responses) were more attenuated than those of higher brain functions, such as those detected in an electroencephalogram. In miniature swine anaesthetized with dexmedetomidine and isoflurane, hypothermia profoundly affected anaesthetic requirement and duration of action of dexmedetomidine (Vainio & Bloor, 1994).

2.4.6 Effects of dexmedetomidine on stress hormones

Dexmedetomidine requires only a slight α_2-adrenoceptor availability to decrease noradrenaline turnover (Rabin et al., 1996b), and very low doses of dexmedetomidine result in sympatholysis (Flacke et al., 1993). Thus, patients in need of a high level of sympathetic tone to maintain blood pressure may not tolerate even low doses of dexmedetomidine (Bloor et al., 1992a). However, in postoperative patients, sympathetic tone was not entirely abolished by dexmedetomidine infusion, and merely the unwanted increases in heart rate and blood pressure were attenuated (Talke et al., 1997). Very high doses of dexmedetomidine have been shown to inhibit steroidogenesis in dogs, the peak effect following the peak hypnotic action, but a biologically important influence on steroidogenesis is considered unlikely (Maze et al., 1991). Dexmedetomidine infusion did not inhibit adrenal steroidogenesis in humans after major surgery (Venn et al., 2001).

2.4.6.1 Effects of dexmedetomidine on stress hormones in humans

Dexmedetomidine dose-dependently decreased plasma noradrenaline levels up to 90% (Kallio et al., 1989; Aantaa et al., 1990a; b, 1991b; Bloor et al., 1992b; Scheinin H et al., 1992; Jaakola et al., 1994; Lawrence & DeLange, 1997; Ebert et al., 2000), and plasma adrenaline levels were usually decreased as well (Bloor et al., 1992a; Scheinin H et al., 1992; Lawrence & DeLange, 1997; Ebert et al., 2000). The effect of dexmedetomidine on cortisol and beta-endorphin levels has received less attention. Cortisol levels have been shown to be unaffected by dexmedetomidine (Kallio et a.l, 1989; Aantaa et al., 1990b) or increased less after dexmedetomidine than after placebo in response to surgery (Aho et al., 1992b). Plasma levels of beta-endorphin followed a similar pattern (Aho et al., 1992b).

2.4.6.2 Effects of dexmedetomidine on stress hormones in dogs

Iv dexmedetomidine has been shown to decrease catecholamine levels in dogs (Schmeling et al., 1991; Bloor et al., 1992b; Flacke et al., 1993; Roekaerts et al., 1996, 1997; Willigers et al., 2003). Very high dexmedetomidine doses have been reported to release catecholamines from cardiac stores in dogs (Flacke et al., 1992). In dogs undergoing thoracic surgery (induced myocardial ischaemia), infusion of dexmedetomidine 0.6 µg/kg/h had no effect on plasma cortisol levels (Willigers et al., 2003).

Clinical doses of im racemic medetomidine had no influence on canine cortisol levels (Ambrisko & Hikasa, 2002) but delayed the cortisol response induced by ovariohysterectomy (Benson et al., 2000; Ko et al., 2000). After thoracotomy, catecholamine levels were lower in dogs receiving im medetomidine than in those receiving buprenorphine (Vainio & Ojala, 1994). In dogs undergoing ovariohysterectomy, catecholamine and cortisol levels were lower after im medetomidine than after acepromazine premedication; however, the concentration of beta-endorphin did not differ between the premedicant groups (Väisänen et al., 2002).

2.4.7 Adverse effects caused by dexmedetomidine

In humans, dexmedetomidine has generally been well tolerated (Kallio et al., 1989; Aantaa et al., 1990a, 1990b; Jaakola et al., 1991; Bloor et al., 1992b; Aho et al., 1992b; Scheinin H et al., 1992; Jaakola, 1995). Fatigue, decreased salivation (Kallio et al., 1989; Aantaa et al., 1990a, 1990b), nausea (Venn et al., 1999), discomfort and agitation (Dutta et al., 2000; Ebert et al., 2000) have been described in single cases after dexmedetomidine.

In dogs, hypothermia, muscular twitching and vomiting are the most commonly described adverse effects after medetomidine administration (Vainio, 1989; England & Clarke, 1989; Hamlin & Bednarski, 1989).

2.5 Levomedetomidine

Levomedetomidine is considered to be pharmacologically inactive (MacDonald et al., 1991, Savola & Virtanen, 1991, Aantaa et al., 1993). However, it has been shown to be involved in kinetic drug interactions by prolonging the hepatic metabolism of hexobarbital (Pelkonen et al., 1991), alfentanil (Kharasch et al., 1991) and ketamine (Kharasch et al., 1992). In a radioligand assay, levomedetomidine bound similarly to all α_2-adrenoceptor subtypes but with a lower affinity than dexmedetomidine (Jansson et al., 1994). Levomedetomidine is also capable of binding to and activating α_1-adrenoceptors, albeit more weakly than dexmedetomidine (Schwinn et al., 1991). The α_2- to α_1-adrenoceptor selectivity ratio

reported for dexmedetomidine is 1300, whereas that of levomedetomidine is 23 (Aantaa et al., 1993). Levomedetomidine has been shown to have affinity towards cerebral imidazoline-receptors as well but again, less than dexmedetomidine (Wikberg et al., 1991). Levomedetomidine was as efficacious as dexmedetomidine in blocking adrenocorticotrophic hormone (ACTH) -stimulated corticosterone production in vitro, suggesting that the imidazole structure and not the anaesthetic potency led to inhibition of steroidogenesis (Maze et al., 1991).

In vitro studies have demonstrated that levomedetomidine may act as a weak partial α_2-adrenoceptor agonist (Jansson et al., 1994) or as an inverse α_2-adrenoceptor agonist (negative antagonist), depending on the test system and the constitutive activity of the receptors (Jansson et al., 1998). It inhibited the contraction of the rat vas deferens, the maximum response being 30% of that to dexmedetomidine (Jansson et al., 1998). The enantiomers showed opposite effects on signal transduction through the α_{2A}-adrenoceptor. Dexmedetomidine acted as an agonist by elevating Ca^{2+} and inhibiting cAMP production, and levomedetomidine acted as an inverse agonist by reducing Ca^{2+} and enhancing cAMP production. Both effects were abolished by pertussis toxin, suggesting transduction through pertussis toxin- sensitive G-proteins (Jansson et al., 1998).

In vivo studies of the effects of levomedetomidine are scarce. Cardiorespiratory changes associated with levomedetomidine have not been reported, and the behavioural alterations that have been published are difficult to interpret. Levomedetomidine (99.7% optical purity) has been claimed to have some sedative and analgesic properties at very high doses in rats (Savola & Virtanen, 1991). It was shown to prolong sleeping time in rats sedated with hexobarbital (Pelkonen et al., 1991; Savola & Virtanen, 1991), probably due to kinetic interaction (Pelkonen et al., 1991). In rats, ip levomedetomidine 10, 30 and 100 µg/kg had no effect on the MAC of halothane (Segal et al., 1988) and it was without hypnotic effects even at a dose of 30 mg/kg ip (Doze et al, 1989a), however, a dose of 10 mg/kg sc provoked arousal (MacDonald et al., 1991). In mice, ip levomedetomidine (100 and 300 µg/kg) increased cGMP content, while dexmedetomidine decreased it at doses that typically cause sedation (Vulliemoz et al., 1996). In tadpoles, levomedetomidine showed some anaesthetic effects and adhered to the Meyer-Overton correlation (Tonner et al., 1997).

Schmeling et al. (1991) demonstrated that low (< 5 µg/kg iv) doses of levomedetomidine did not alter the haemodynamics, arterial blood gas tensions or noradrenaline plasma concentrations in conscious dogs. Administration of 1, 3 or 10 µg/kg of levomedetomidine iv had no effect on the haemodynamics or MAC in halothane-anaesthetized dogs (Vickery et al., 1988). Levomedetomidine 0.2 or 0.5 µg/kg/min did not affect the arrhythmogenic dose of adrenaline in dogs under halothane anaesthesia, while dexmedetomidine increased the arrhythmogenic threshold (Hayashi et al., 1991). In rats, iv levomedetomidine (0.1 to 10 mg/kg, 99.7% optical purity) did not change blood pressure or heart rate (Savola & Virtanen, 1991), and doses of 1 µg administered intracranially or 50 µg/kg administered iv had no effect on the rostral ventrolateral medulla activity or blood pressure (Hong et al., 1992). Medetomidine and dexmedetomidine induced a mydriatic response in rats, but levomedetomidine was inactive (Savola & Virtanen, 1991).

2.6 Medetomidine-dexmedetomidine comparisons in different species

In rats, the following half-maximal effects were obtained after iv medetomidine and dexmedetomidine: decreased heart rate (at doses of 0.4 and 0.5 µg/kg for medetomidine and dexmedetomidine, respectively), decreased arterial pressure (1.0 and 0.6 µg/kg), reduced motility (35 and 20 µg/kg), prolonged hexobarbital sleeping time (30 and 20 µg/kg), analgesic properties (20 and 10 µg/kg) and mydriatic response (4 and 2 µg/kg) (Savola & Virtanen, 1991). In cats, while the duration of sedation was shorter after im dexmedetomidine 50 µg/kg than after medetomidine 100 µg/kg, it was longer after dexmedetomidine 75 µg/kg than after medetomidine 150 µg/kg (Ansah et al., 1998). When dexmedetomidine and medetomidine were administered to cats as an infusion at three dose levels, no significant differences were observed between the drugs for sedation, analgesia, muscular relaxation and heart and respiratory rates (Ansah et al., 2000). In sheep undergoing orthopaedic surgery, premedication with iv dexmedetomidine 5 µg/kg or medetomidine 10 µg/kg had the same effects on isoflurane requirements and cardiopulmonary parameters (Kästner et al., 2001a). Im dexmedetomidine 15 µg/kg or medetomidine 30 µg/kg resulted in similar isoflurane requirements in sheep, but heart rate was higher and the partial pressure of oxygen less variable in the dexmedetomidine group (Kästner et al., 2001b).

2.7 Current knowledge of dexmedetomidine and levomedetomidine in dogs

Published studies of dexmedetomidine and levomedetomidine in dogs are presented in Table 1. The doses of dexmedetomidine vary between 0.1 and100 µg/kg, and those of levomedetomidine between 1 and 10 µg/kg. The route of administration has usually been iv, and most of the studies have been conducted while dogs were anaesthetized. The effects of dexmedetomidine and medetomidine have not been compared in conscious dogs. No studies exist in which dexmedetomidine has been used as a sedative and premedicant in dogs clinically, similar to medetomidine. Moreover the sedative, analgesic and cardiovascular effects of dexmedetomidine and levomedetomidine in conscious dogs remain unknown. While the pharmacokinetics of medetomidine in dogs has been reported (Salonen 1989), the pharmacokinetics of dexmedetomidine and levomedetomidine in dogs is yet to be determined. The recovery profile after dexmedetomidine premedication and the pharmacological effect of levomedetomidine in dogs also remain obscure. The effects of dexmedetomidine and levomedetomidine on the adrenaline arrhythmic threshold during halothane anaesthesia have been revealed, but no other reports are available on ECG findings after administration of these drugs.

Table 1

Published studies of dexmedetomidine in dogs

- **Doses, administration routes and other drugs**

1. Vickery et al., 1988 (1, 3 and 10 µg/kg iv/20 min, cumulative, under halothane)
2. Flacke et al., 1990 (1-30 µg/kg iv bolus or over 20 min, cumulative, under isoflurane)
3. Zornow et al., 1990 (10 µg/kg iv/10 min, under isoflurane)
4. Schmeling et al., 1991 (1.25, 2.5 and 5 µg/kg iv/10min, cumulative, conscious)
5. Maze et al., 1991 (80 µg/kg im/sc, conscious)
6. Proctor et al., 1991 (10 and 20 µg/kg per os, conscious and before enflurane)
7. Hayashi et al., 1991 (0, 0.1, 0.2 and 0.5 µg/kg/min infusion, under halothane)
8. Karlsson et al., 1990 (10 µg/kg iv/15 min, under halothane)
9. Bloor et al., 1992 (20 µg/kg iv/2 min, under isoflurane)
10. Nguyen et al., 1992 (1,10, 20 and 100 µg/kg iv, conscious and 3 µg/kg iv under isoflurane)
11. Gregoretti et al., 1992 (3 and 30 µg/kg iv, under halothane)
12. Proctor et al., 1992 (20 µg/kg per os, conscious and before propofol, ketamine and etomidate)
13. Flacke et al., 1993 (0.25, 0.5, 1.0, 2.0 and 4.0 µg/kg iv, cumulative, under isoflurane)
14. Kersten et al., 1993 (30 µg/kg per os, conscious and before isoflurane and desflurane)
15. Sabbe et al., 1994 (1, 3 and 10 µg/kg iv (+ intrathecal, epidural, intracisternal))
16. Salmenperä et al., 1994 (0.1-10 µg/kg iv cumulative, under enflurane and enflurane and fentanyl)
17. Kamibayashi et al., 1995a (0, 0.2, 0.5 µg/kg/min infusion, under halothane)
18. Kamibayashi et al., 1995b (0.5 µg/kg/min infusion, under halothane)
19. Ishiyama et al., 1995 (topical application to pial vessels)
20. Lawrence et al., 1996a (0.1, 1 and 10 µg/kg iv/2 min, cumulative, under fentanyl/halothane and chloralose/urethane)
21. Lawrence et al., 1996b (0.1, 0.3, 1, 3 and 10 µg/kg iv/2 min, cumulative, under fentanyl/halothane and chloralose/urethane)
22. Roekaerts et al., 1996 (1 and 3 µg/kg iv, under halothane)
23. Roekaerts et al., 1997 (0.1, 0.3, 1.0, 3.0 and 10 µg/kg iv/1 min, cumulative, under fentanyl)
24. Pagel et al., 1998a (1, 2.5, 5 µg iv cumulative, conscious)
25. Pagel et al., 1998b (5 µg/kg iv, conscious)
26. Kaivosaari et al., 2002 (liver microsomes)
27. Willigers et al., 2003 (0.6 µg/kg/h infusion, under halothane)

- **Sedative effects** 15
- **Analgesic effects** 15
- **Anaesthetic-sparing effects** 1, 9, 10, 16
- **Cardiovascular effects, anaesthetized dogs** 1, 2, 3, 6, 8, 9, 11, 12, 13, 14, 16, 20, 21, 22, 23, 27
- **Cardiovascular effects, conscious dogs** 4, 6, 12, 14, 24, 25
- **Respiratory effects, anaesthetized dogs, controlled ventilation** 1, 6
- **Respiratory effects, anaesthetized dogs, spontaneous ventilation** 10
- **Respiratory effects, conscious dogs** 4, 6, 10, 15
- **Pharmacokinetics** 15 (in cerebrospinal fluid), 26 (glucuronidation)
- **Recovery** 6, 27
- **Arrhythmias** (adrenaline threshold) 7, 17, 18
- **Stress hormones, anaesthetized dogs** 2, 6, 9, 13, 14, 22, 23, 27
- **Stress hormones, conscious dogs** 4, 5, 6, 14

Published studies of levomedetomidine in dogs

- **Doses, administration routes and other drugs**

1. Vickery et al., 1988 (1, 3 and 10 µg/kg iv/20 min, cumulative, under halothane)
4. Schmeling et al., 1991 (1.25, 2.5 and 5 µg/kg iv/10 min, cumulative, conscious)
7. Hayashi et al., 1991 (0.2 and 0.5 µg/kg/min infusion, under halothane)

- **Cardiovascular effects** 1, 4
- **Respiratory effects** 1, 4
- **Arrhythmias** (adrenaline threshold) 7
- **Stress hormones** 4
- **Dexmedetomidine-levomedetomidine comparisons** 1, 4
- **Dexmedetomidine-medetomidine comparisons** 1

3. AIMS OF THE STUDY

1) To investigate the clinical effects and pharmacokinetics of medetomidine, dexmedetomidine and levomedetomidine in dogs to determine whether dexmedetomidine offers any benefit over racemic medetomidine (I, II, III).

2) To determine whether levomedetomidine has any pharmacological activity or whether it influences the sedative and analgesic effects of dexmedetomidine in dogs (II).

3) To determine the most appropriate premedicant dose level of dexmedetomidine in dogs (III).

4) To compare clinical responses to propofol infusion and propofol/isoflurane anaesthesia in dexmedetomidine premedicated dogs, both during anaesthesia and the recovery period (IV).

5) To evaluate the suitability of a cold pressor test (CPT) as a stress stimulus using dogs sedated and premedicated with dexmedetomidine as a model (IV).

6) To assess the effects of dexmedetomidine premedication and propofol/isoflurane or propofol infusion anaesthesia on the incidence of arrhythmias in healthy dogs during the perianaesthetic period (V).

4. MATERIALS AND METHODS

4.1 Animals

The same six healthy beagles, three females (dogs 1, 2 and 3) and three males (dogs 4, 5 and 6), were used. The dogs were aged from 10 months to 3 years during the studies. The males were castrated before Study II and females were ovariohysterectomized before Studies IV and V. The dogs were not used for any other purposes. They were group-housed and received outdoor exercise daily. They were regularly vaccinated and dewormed. Dogs 2 and 3 were littermates, as were dogs 4 and 6. Before starting the experiments, the dogs were trained to handling and adapted to the study rooms.

4.2 Drugs and dosages

The effects of medetomidine (Domitor, Orion Pharma, Turku, Finland), dexmedetomidine (Orion Pharma) and levomedetomidine (Orion Pharma) were studied. All drugs were in the form of hydrochlorides. The study designs are summarized in Table 2.

Study I: Each dog was studied six times on separate days. Medetomidine 40 µg/kg, dexmedetomidine 20 µg/kg, dexmedetomidine 10 µg/kg, levomedetomidine 20 µg/kg, levomedetomidine 10 µg/kg and saline placebo were administered as an iv bolus.

Study II: Each dog was studied three times on separate days. The dogs were administered a low dose of levomedetomidine (10 µg/kg) as an iv bolus, followed by infusion at a dose of 25 µg/kg/h; a high dose of levomedetomidine (80 µg/kg), followed by infusion at a dose of 200 µg/kg/h; and saline, followed by saline infusion. The infusions were continued for 120 minutes, and at 60 minutes, 10 µg/kg of dexmedetomidine was administered as an iv bolus.

Study III: Each dog was studied six times on separate days. Medetomidine 0.4 µg/kg, 4 µg/kg and 40 µg/kg and dexmedetomidine 0.2 µg/kg, 2 µg/kg and 20 µg/kg were administered as an iv bolus as premedication preceding a light level of propofol/isoflurane anaesthesia.

Studies IV and V: Each dog was studied six times on separate days. Dexmedetomidine 10 µg/kg was administered im as premedication before propofol/isoflurane (end tidal 1.0%; twice) or propofol infusion (200 µg/kg/min; twice) anaesthesia or premedication alone (twice).

4.3 Clinical signs of sedation, analgesia and anaesthesia

The effects were evaluated subjectively by the main investigator (E.K). The scoring of sedative and analgesic effects in Study III in presented in Table 3. The scoring systems were not exactly the same in Studies I, II and III. The sedative effects were assessed by observing spontaneous posture, palpebral reflex, position of eye, relaxation of jaws and tongue, response to sound (I, II), resistance when laid laterally recumbent and general appearance (Clarke & England, 1989; Vainio et al., 1989). The analgesic effect was assessed by pinching the interdigital skin of a hind foot to observe withdrawal reflex (Clarke & Enland, 1989; Sabbe et al., 1994; Quandt et al., 1998).

The depth of anaesthesia was determined by observing the ocular reflexes and eye position, relaxation of jaws and tongue, and motoric, haemodynamic and respiratory

Table 2. Summary of the study designs.

Study	Number of dogs	Design	Control drug	Drugs, doses and routes of administration	Monitoring
I	6	Randomized 6x6 Latin square Blinded Placebo-controlled	Saline	Med 40 µg/kg iv Dex 10 and 20 µg/kg iv Levo 10 and 20 µg/kg iv	Sedation, analgesia, cardiorespiratory parameters, Dex and Levo plasma concentrations, noradrenaline, adrenaline
II	6	Randomized 6x3 cross-over Blinded Placebo-controlled	Saline	Levo 10 µg/kg iv + 25 µg/kg/h + Dex 10µg/kg iv Levo 80 µg/kg iv + 200 µg/kg/h + Dex 10 µg/kg iv	Sedation, analgesia, cardiorespiratory parameters, Dex and Levo plasma concentrations, noradrenaline, adrenaline
III	6	Randomized 6x6 Latin square Blinded for the drug		Med 0.4, 4.0 and 40 µg/kg iv ** Dex 0.2, 2.0 and 20 µg/kg iv **	Sedation, analgesia, cardiorespiratory parameters, propofol dose, end-tidal isoflurane concentration, recovery
IV	6	Randomized 6x6 Latin square		Dex 10 µg/kg im ***	Depth of anaesthesia, cardiorespiratory parameters, noradrenaline, adrenaline, beta-endorphin, cortisol, recovery, cold pressor test
V *	6	Randomized 6x6 Latin square		Dex 10 µg/kg im***	Holter

Med = medetomidine, Dex = dexmedetomidine, Levo = levomedetomidine
* Material for Study V was collected during Study IV
** Propofol/isoflurane anaesthesia
*** Propofol/isoflurane or propofol infusion anaesthesia

Table 3.

Scoring of sedation in Study III

1. Position
   0 Standing, 1 Standing but staggers, 2 Sternal head up, 3 Sternal head down, 4 Lateral head down
2. Palpebral reflex
   0 Normal, 1 Slightly reduced, 2 Weak, 3 Absent
3. Position of the eye
   0 Middle, 2 Turned down
4. Jaw and tongue relaxation
   0 Normal, opens the jaws but resists manipulation of the tongue, 1 Bites jaws together, 2 Opens the jaws but strong resistance when tongue is pulled, 3 Slight resistance when tongue is pulled, 4 No resistance when tongue is pulled
5. Resistance to positioning in lateral recumbency
   0 Normal, 1 Turns back to sternal position, 2 Some resistance but stays in lateral position, 3 No resistance or the position is already lateral
6. General appearance
   0 Normal, 1 Slightly tired, head drooping, 2 Mild sedation, reacts clearly to surroundings, 3 Moderate sedation, reacts mildly to surroundings, 4 Deep sedation, no reaction to surroundings

Scoring of analgesia in Study III

0 Normal pedal reflex, immediate withdrawal, 1 Slow reflex, 2 Withdrawal of foot only after pinching with increased intensity for 3 seconds, 3 No response
The effect was tested by pinching the interdigital skin of an extended hind foot. To avoid unnecessary pain, pinching was initiated lightly with fingernails and stopped immediately when a pedal reflex was induced.

responses to noxious stimulus (interdigital pinching in Study III). In Study III, the dogs were kept in a light plane of anaesthesia, which was characterized by lack of purposeful movement in response to interdigital pinching for 3 seconds, moderate relaxation of the jaws, eye rotation, and presence of a palpebral reflex. Noxious stimulus was applied every 5 minutes. If there was no haemodynamic or respiratory response to pinching, concentration of isoflurane was slightly decreased. If the dog flexed its leg or moved its head or tongue, concentration of isoflurane was slightly increased.

4.4 Cold pressor test

In Study IV, the suitability of a cold pressor test (CPT) (Short & Paddleford, 1996; Short, 1999; Ebert et al., 2000; Hall et al., 2000) as a noxious stimulus was evaluated. Dogs were premedicated with im dexmedetomidine 10 µg/kg and tested every 15 minutes during

dexmedetomidine sedation, propofol/isoflurane anaesthesia and propofol infusion anaesthesia, starting before induction. CPT was performed by dipping the front leg to the level of the carpal joint in 0°C ice water for one minute or until the dog lifted the paw. The dog was not moved during testing. Cardiorespiratory parameters and level of anaesthesia were determined and blood samples were taken before the stimulus. The cardiorespiratory parameters were rerecorded immediately after the stimulus, and the difference was used to show the immediate effect of CPT.

4.5 Cardiorespiratory effects

Heart rate and direct blood pressure were monitored via a catheter in a femoral artery. Timed lead II electrocardiograms were recorded in Studies I and II. The recordings were analysed mainly for heart rate and incidence of atrioventricular (AV) blocks and ventricular premature contractions (VPC). AV-blocks were defined as follows (Tilley 1992):

First-degree AV-block: the P-R interval is longer than 0.13 seconds.

Second-degree AV-block: one or more P waves are not followed by QRS-T complexes. No attempt was made to classify these to Mobitz type I or II.

Sinus pause was defined as a pause greater than twice the normal R-R interval.

Continuous perianaesthetic 24-hour Holter recordings were made in Study V. The electrodes were placed around the dog's chest, and the recorder was placed in the pocket of a jacket designed for this purpose. The amount of VPCs, second and third degree AV-blocks, and mean heart rate/hour were counted and the longest sinus pauses were reported.

Respiratory rate was calculated by observing the movements of the dog's chest (I-IV) or by using a monitor (III and IV). Arterial blood samples were taken from the catheter for immediate blood gas analysis in Studies I-IV. In addition, plasma lactate concentration was determined in Study IV. Arterial haemoglobin saturation was estimated in Study III by using a pulse oximeter.

4.6 Pharmacokinetic studies

Blood samples for plasma drug (medetomidine, dexmedetomidine, or levomedetomidine) concentration determinations were collected in Studies I and II. The samples were obtained from an arterial catheter, and plasma was separated, frozen and later analysed by capillary gas chromatography with mass spectrometry detection. In Study I, total clearance, volume of distribution at steady state and terminal half-life were calculated for each drug and dosage.

4.7 Stress hormone studies

In Studies II and IV, plasma adrenaline and noradrenaline concentrations were determined, as well as plasma beta-endorphin and cortisol concentrations in Study IV. All samples were obtained via an arterial catheter. A catecholamine assay was done using high-performance liquid chromatography. Beta-endorphin and cortisol concentrations were analysed by radioimmunoassay. Baseline plasma beta-endorphin concentration in these beagles was measured separately by obtaining jugular venous blood samples twice in each dog.

4.8 Statistical analyses

Numerical variables were analysed by use of repeated-measures analysis of variance (ANOVA), and categorical variables were analysed by use of the non-parametric Friedman test (I-III) or Cochran-Mantel-Haenszel test (IV). Values of $P<0.05$ were considered significant. Data are expressed as mean ± standard deviation (SD). Additionally, 95% confidence intervals (CI) were calculated for some of the main results.

5. RESULTS

5.1 Clinical signs of sedation, analgesia and anaesthesia

5.1.1 Effects of medetomidine and dexmedetomidine on clinical signs of sedation and analgesia (I, II, IV)

The overall level of sedation did not differ between iv medetomidine 40 µg/kg, dexmedetomidine 20 µg/kg and dexmedetomidine 10 µg/kg during the first hour (Figure 3). Sedation caused by the higher dose of dexmedetomidine lasted longer than that of dexmedetomidine 10 µg/kg. The dogs stayed laterally recumbent longer after dexmedetomidine 20 µg/kg than after medetomidine 40µg/kg or dexmedetomidine 10 µg/kg. All treatments caused significant analgesia, but analgesia lasted longer after dexmedetomidine 20 µg/kg than after medetomidine 40 µg/kg or dexmedetomidine 10 µg/kg (I). In Study III, the effects of iv medetomidine and dexmedetomidine were similar with respect to sedation and analgesia 10 minutes after administration. After receiving the higher doses (40 and 20 µg/kg for medetomidine and dexmedetomidine, respectively), the dogs were deeply sedated and showed good analgesia. Doses 4 and 2 µg/kg caused moderate sedation and light analgesia respectively. Doses 0.4 and 0.2 µg/kg caused very slight sedation and no analgesia, respectively. In Study IV, the dogs were recumbent after im dexmedetomidine 10 µg/kg in a mean time of 11.9 ± 3.5 minutes.

5.1.2 Cold pressor test (IV)

During im dexmedetomidine sedation one female dog responded to CPT every time and two other females once by withdrawing the paw from ice water. Respiratory rate increased before induction and 15 minutes after induction in response to CPT (IV).

5.1.3 Effects of levomedetomidine on clinical signs of sedation and analgesia (I, II)

An iv bolus of levomedetomidine (10 or 20 µg/kg) or placebo did not cause any apparent signs of sedation or analgesia. However, two dogs seemed somewhat tired although standing after administration of levomedetomidine 10 µg/kg, and one dog appeared slightly nervous after levomedetomidine 20 µg/kg (I). In Study (II), levomedetomidine (10 or 80 µg/kg iv followed by continuous infusion at a dose of 25 µg/kg/h or 200 µg/kg/h, respectively) or placebo caused no observable signs of sedation, analgesia or behavioural changes. The overall degree of sedation was higher when dexmedetomidine was given alone than when given in combination with either dose of levomedetomidine (Figure 4). The analgesic effect was more profound with dexmedetomidine alone than with dexmedetomidine combined with the higher dose of levomedetomidine.

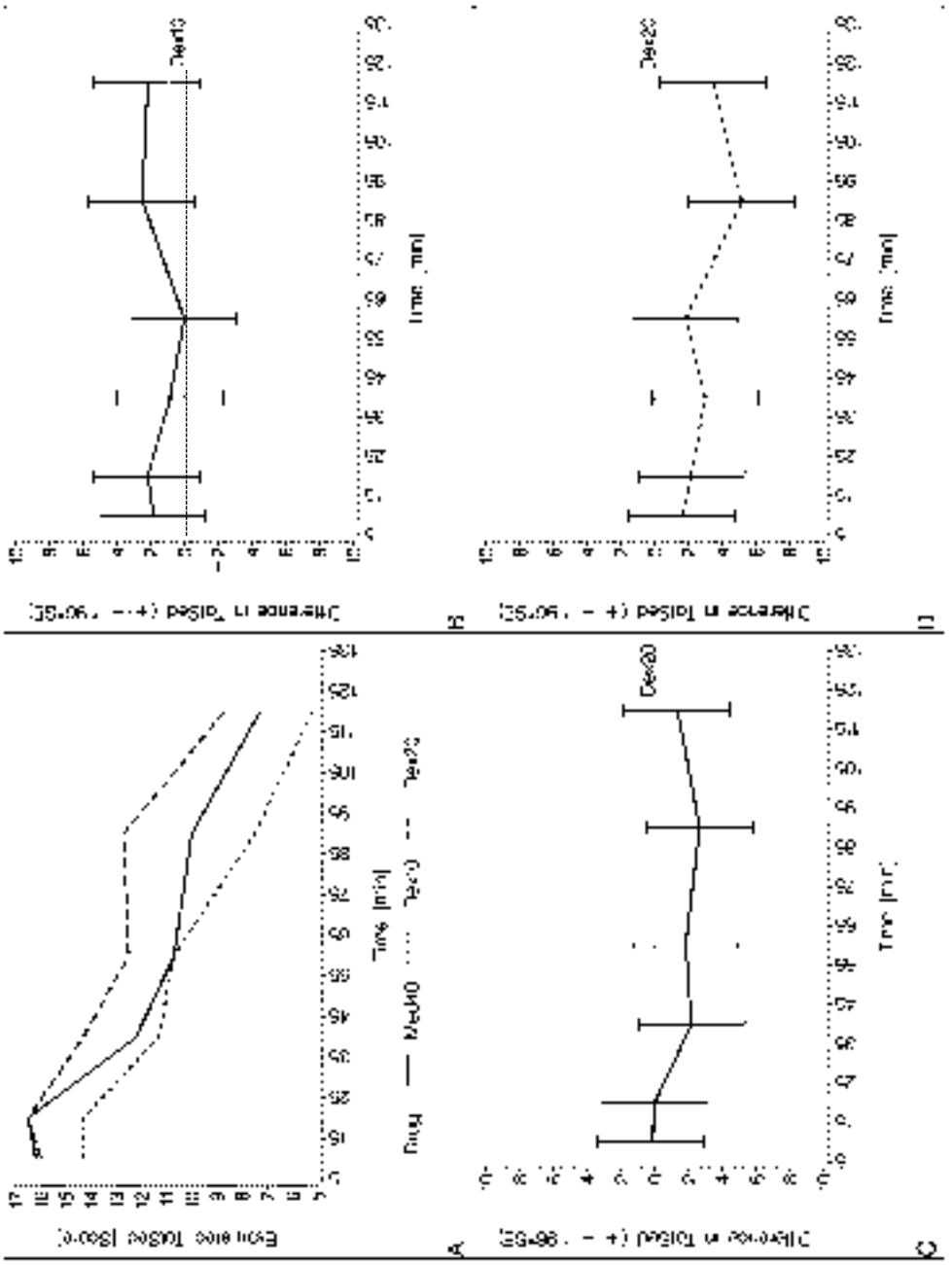

Figure 3
Estimated total sedation (TotSed) scores (A) and estimated difference with 95% CI between medetomidine 40 µg/kg (Med40) and dexmedetomidine 10 µg/kg (Dex10) (B); between medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg (Dex20) (C); between dexmedetomidine 10 µg/kg and dexmedetomidine 20 µg/kg (D) after iv dosing in six dogs. (Study I)

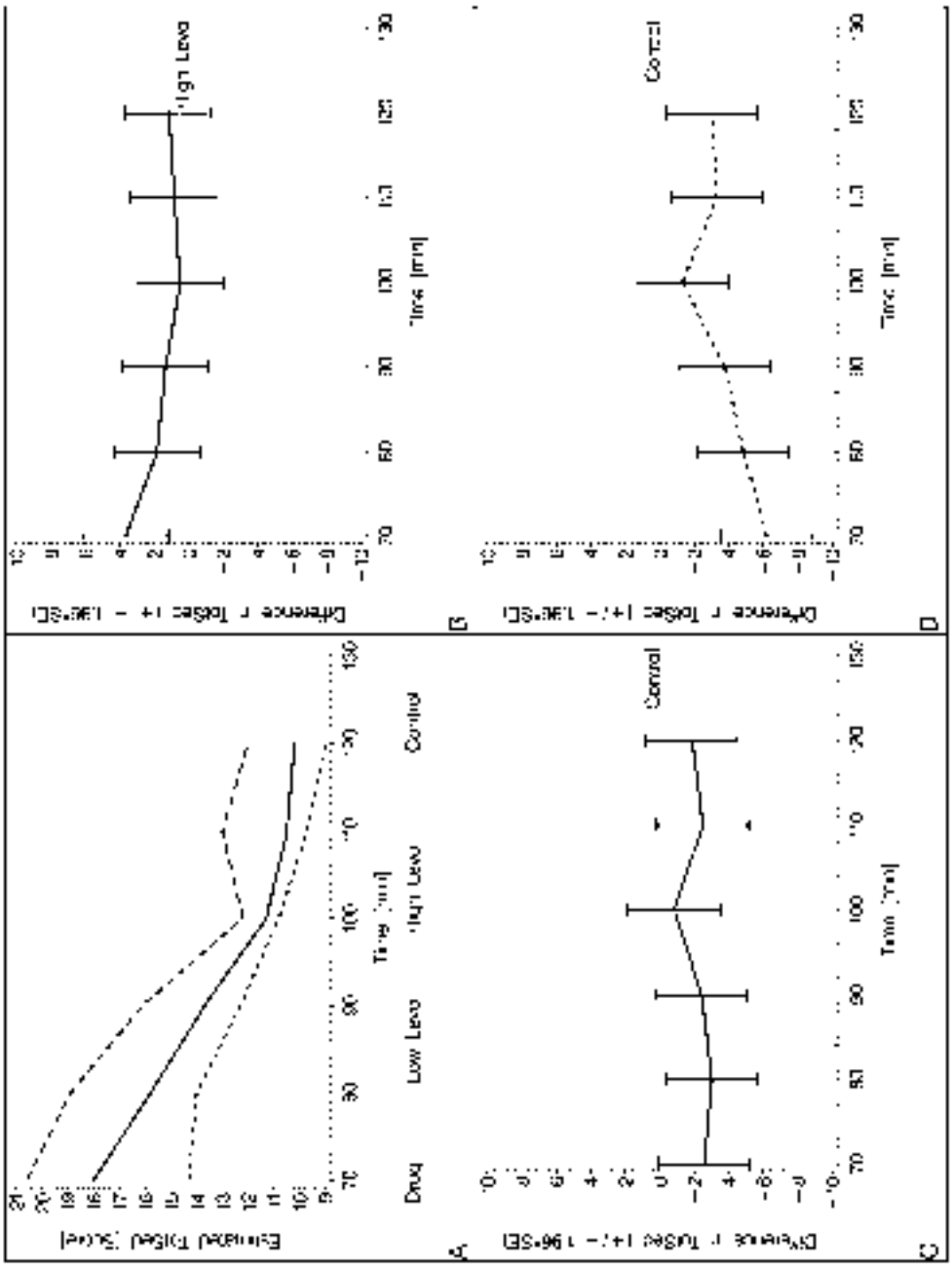

Figure 4
Estimated total sedation (TotSed) scores (A) and estimated difference with 95% CI between iv levomedetomidine 25 µg/kg/h (Low Levo) and levomedetomidine 200 µg/kg/h (High Levo) (B); between levomedetomidine 25 µg/kg/h and saline (Control) (C); between levomedetomidine 200 µg/kg/h and saline (D) in six dogs. The dogs received dexmedetomidine 10 µg/kg iv at 60 minutes. (Study II)

5.1.4 Effects of premedicants on anaesthesia and recovery profile (III, IV)

The amount of propofol required for induction was similar for medetomidine and dexmedetomidine but was affected by the dose level of premedicant. Combined mean end-tidal isoflurane concentration was higher when dogs received iv medetomidine (0.4, 4 and 40 µg/kg), compared with iv dexmedetomidine (0.2, 2 and 20 µg/kg). The overall interaction effect of *drug x dose x time* was not statistically significant. However, the 95% confidence intervals for differences presented in Figure 5 indicates significantly lower isoflurane concentrations for dexmedetomidine 2 µg/kg than for medetomidine 4 µg/kg at certain time-points. Recovery time was prolonged when dogs were treated with iv medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg, as compared with the lower dose levels, but the dogs were always extubated within 10 minutes after the end of anaesthesia (III).

Palpebral reflexes were more distinct when dogs received propofol infusion than during propofol/isoflurane anaesthesia. Recovery times (extubation, head lift, standing) were longer after propofol than after propofol/isoflurane anaesthesia; however, recovery times (head lift, standing) after premedication only were similar to propofol/isoflurane (IV). In both studies (III and IV) recoveries were smooth with no signs of nausea.

5.2 Cardiorespiratory effects

5.2.1 Cardiovascular effects of medetomidine and dexmedetomidine (I-V)

In general, medetomidine and dexmedetomidine had similar effects on the cardiovascular parameters (I, III; Figures 6 and 7). After administration of iv medetomidine 40 µg/kg, dexmedetomidine 20 µg/kg and dexmedetomidine 10 µg/kg arterial blood pressures increased transiently and heart rate decreased (I, II, III). During anaesthesia in Study III, heart rate remained above baseline after premedication with iv medetomidine 0.4 µg/kg /dexmedetomidine 0.2 µg/kg and below baseline with iv medetomidine 4 µg/kg /dexmedetomidine 2 µg/kg or medetomidine 40 µg/kg /dexmedetomidine 20 µg/kg. Overall heart rate was less after iv dexmedetomidine 2 µg/kg compared with the corresponding group medetomidine 4 µg/kg. Arterial blood pressure stayed below reference range during anaesthesia after iv medetomidine 0.4 µg/kg /dexmedetomidine 0.2 µg/kg but was preserved after medetomidine 40 µg/kg /dexmedetomidine 20 µg/kg. In Study IV after premedication with im dexmedetomidine 10 µg/kg, blood pressures stayed within normal reference range during anaesthesia, but the dogs were bradycardic (Figures 8 and 9). Heart rate was lower and blood pressure higher in the propofol than in the propofol/isoflurane group. Blood pressure was similar between propofol and control (dexmedetomidine only) groups, but heart rate was lower in the latter group. Plasma lactate concentration was higher in the propofol/isoflurane group than in the propofol group during anaesthesia, and the highest values were detected in the control group. During recovery heart rate and blood pressures were similar between all treatments. The dogs were bradycardic (< 70 beats/minute) until the end of the recovery monitoring period (5 hours after im dexmedetomidine 10 µg/kg), but blood pressures did not decrease. Bradycardia disappeared when free activity of the dogs was allowed. Mean heart rate was approximately 75 beats/minute during normal sleep in these beagles (V).

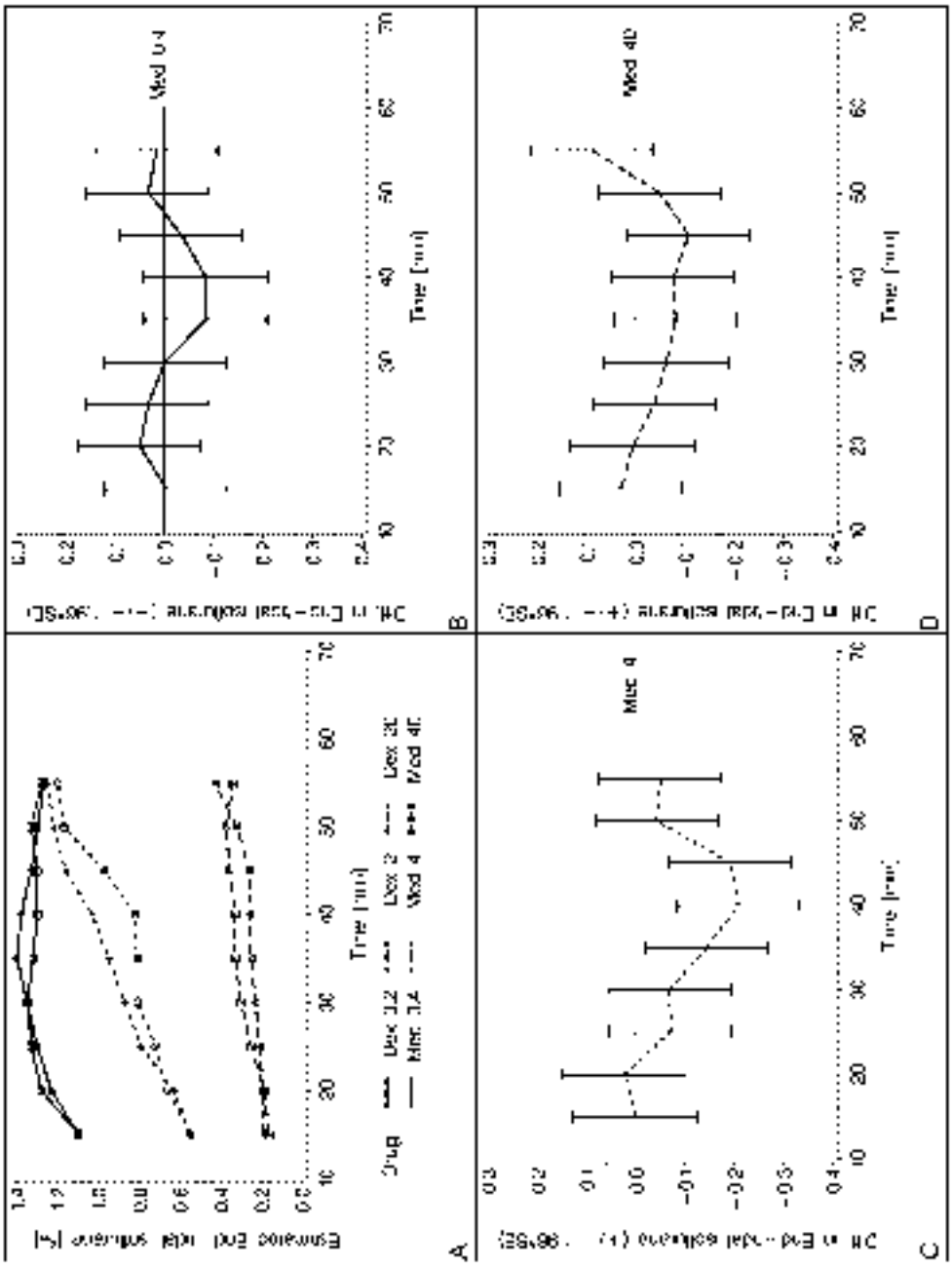

Figure 5
Estimated end-tidal isoflurane concentration (A) and estimated difference with 95% CI between medetomidine 0.4 µg/kg (Med) and dexmedetomidine 0.2 µg/kg (Dex) (B); between medetomidine 4 µg/kg and dexmedetomidine 2 µg/kg (C); and between medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg (D) after iv premedication in six dogs. Anaesthesia was induced with propofol. (Study III)

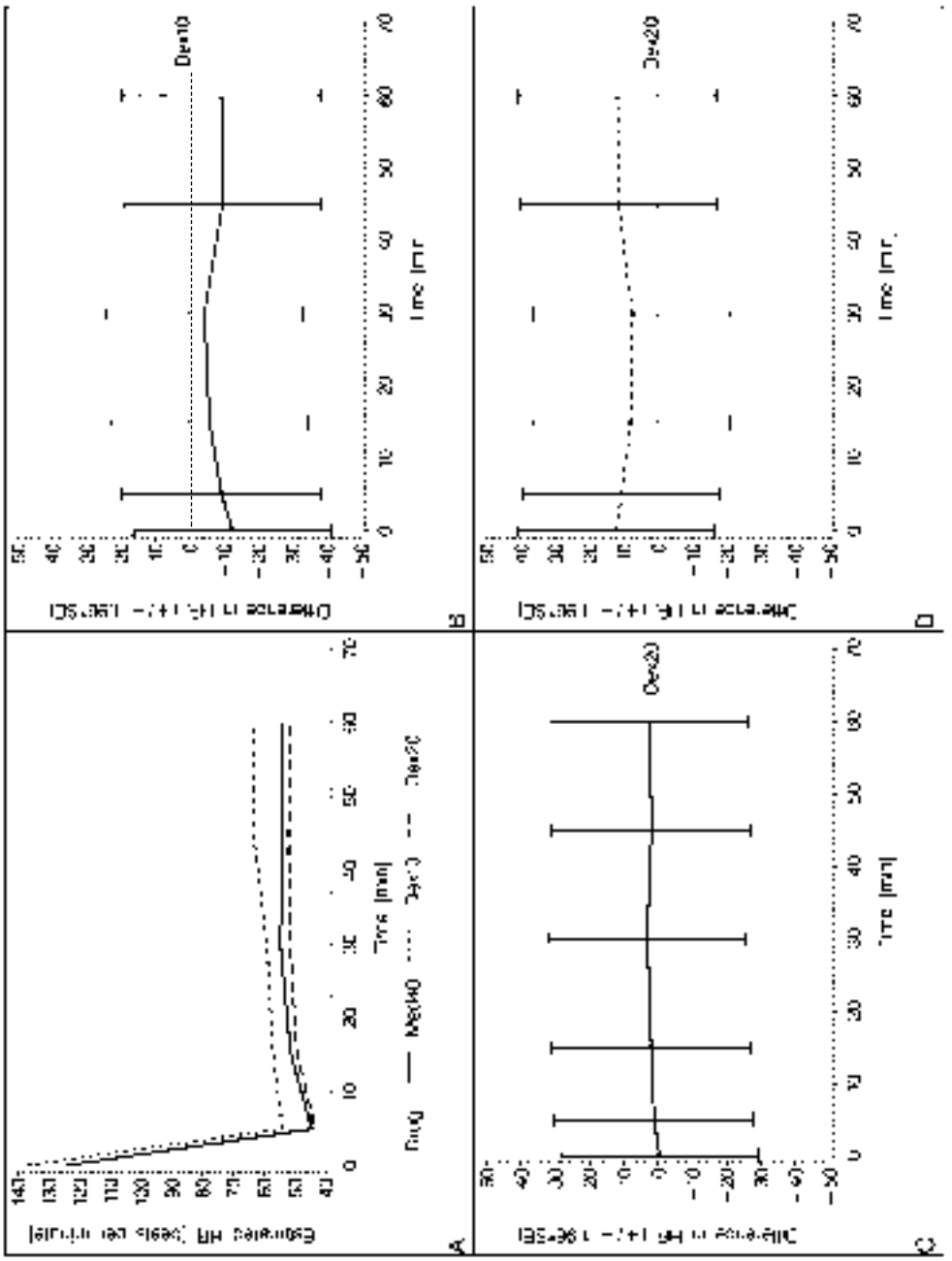

Figure 6
Estimated heart rate (HR) (A) and estimated difference with 95% CI between medetomidine 40 µg/kg (Med40) and dexmedetomidine 10 µg/kg (Dex10) (B); between medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg (Dex20) (C); between dexmedetomidine 10 µg/kg and dexmedetomidine 20 µg/kg (D) after iv dosing in six dogs. (Study I)

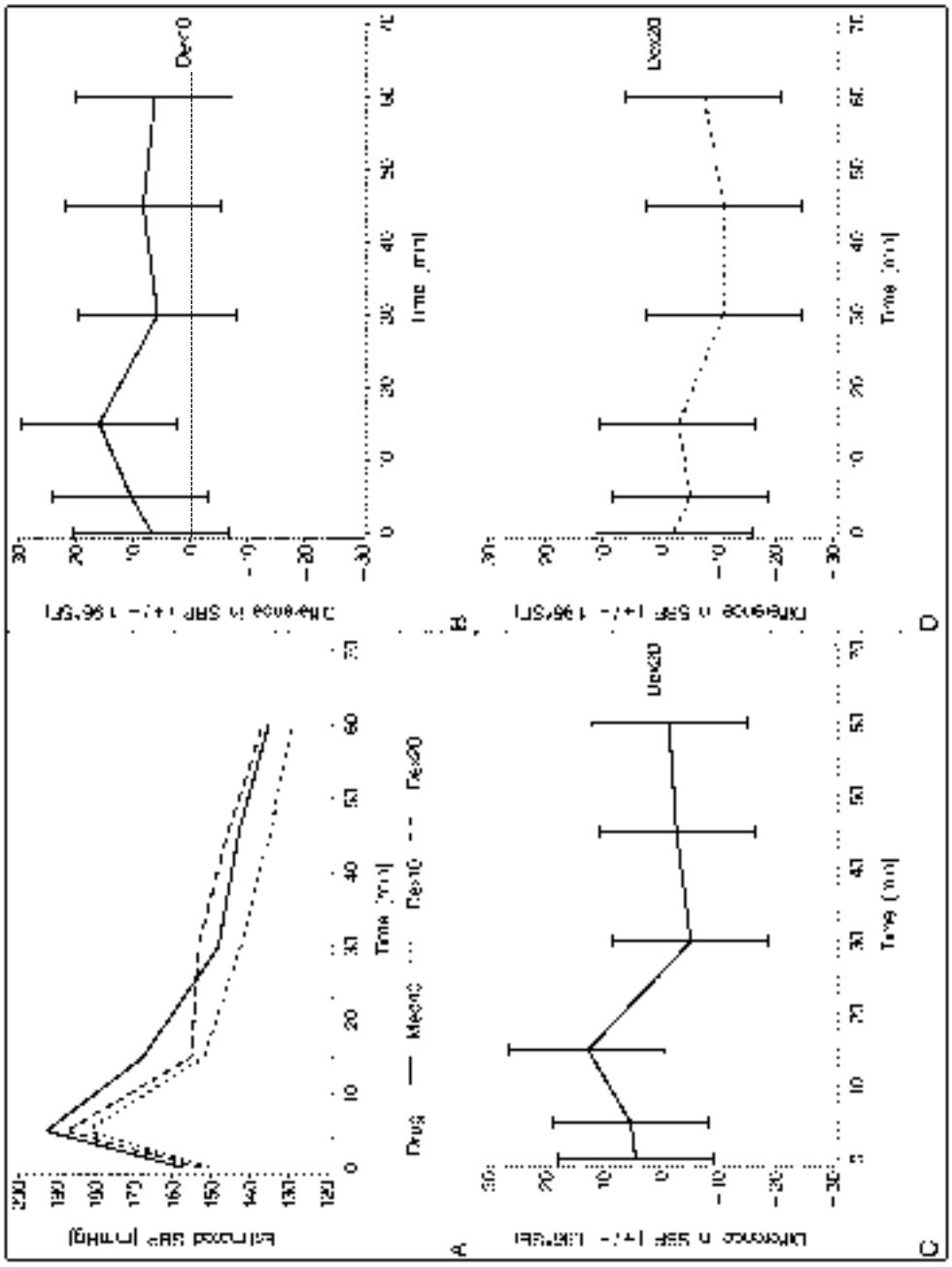

Figure 7
Estimated systolic blood pressure (SBP) (A) and estimated difference with 95% CI between medetomidine 40 µg/kg (Med40) and dexmedetomidine 10 µg/kg (Dex10) (B); between medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg (Dex20) (C); between dexmedetomidine 10 µg/kg and dexmedetomidine 20 µg/kg (D) after iv dosing in six dogs. (Study I)

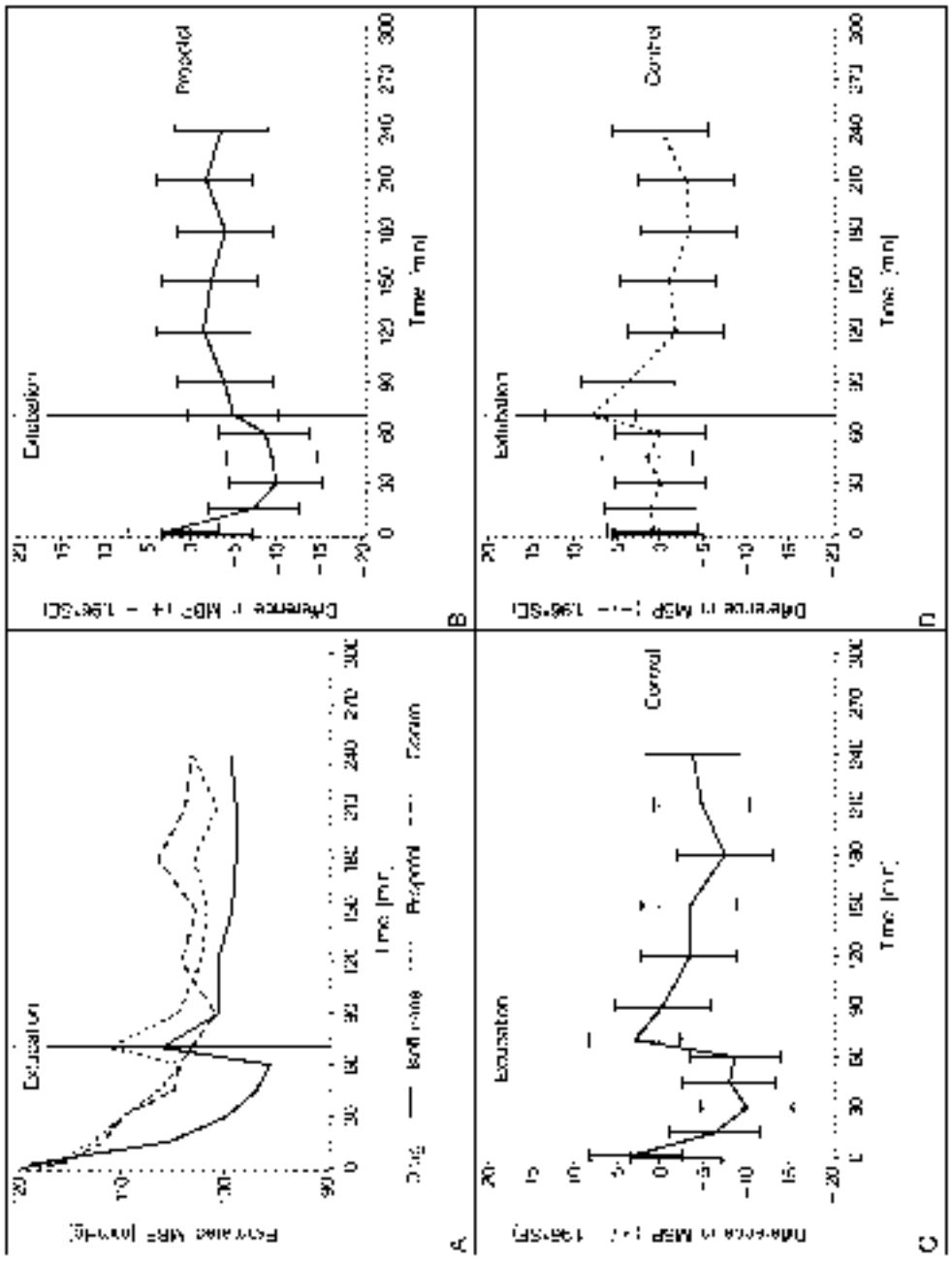

Figure 8
Estimated mean blood pressure (MBP) (A) and estimated difference with 95% CI between the drugs in six dogs treated with isoflurane, propofol or control after premedication with im dexmedetomidine 10 µg/kg of. Isoflurane vs propofol (B); isoflurane vs control (C); propofol vs control (D). (Study IV)

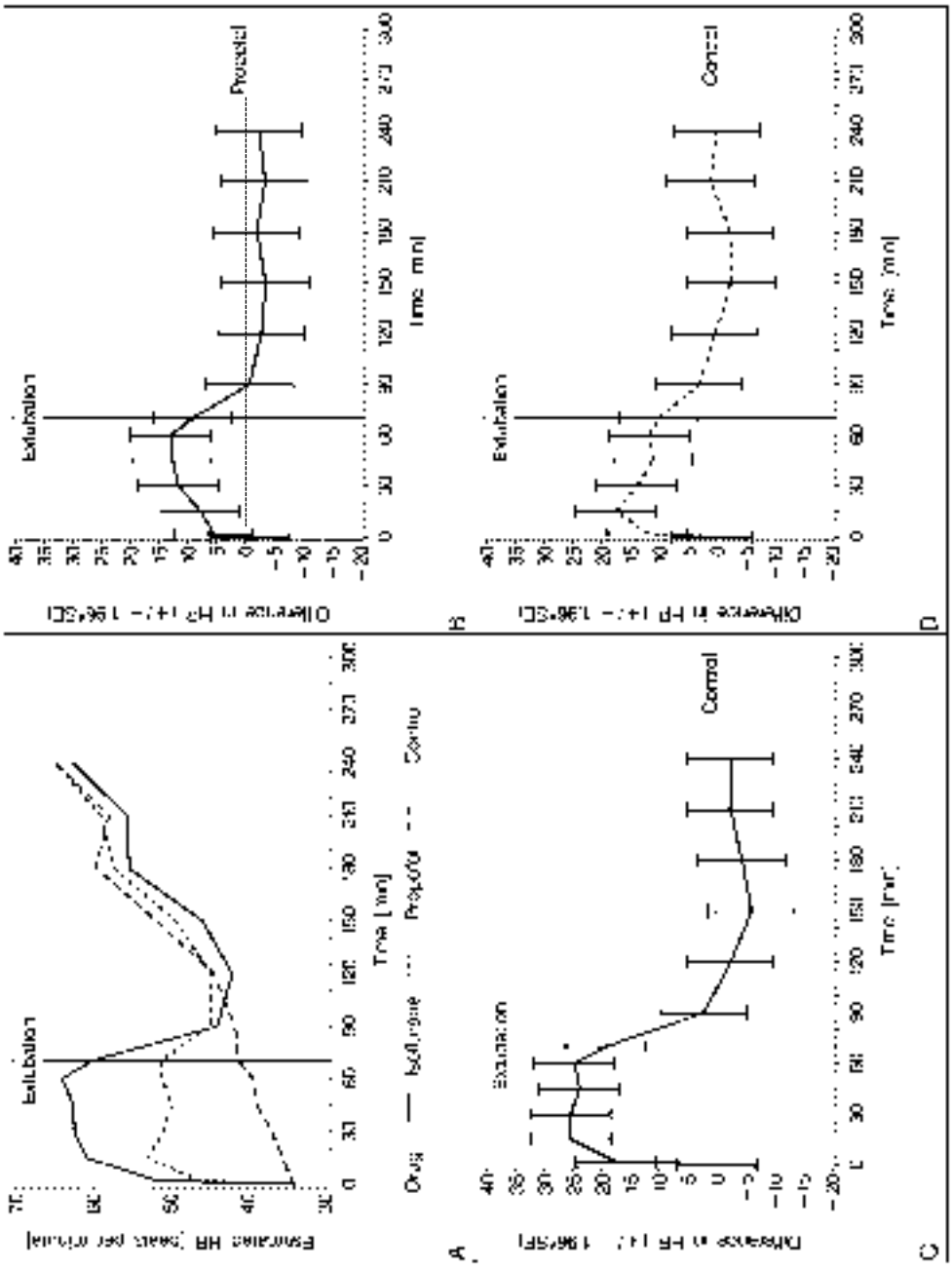

Figure 9
Estimated heart rate (HR) (A) and estimated difference with 95% CI between the drugs in six dogs treated with isoflurane, propofol or control after premedication with im dexmedetomidine 10 µg/kg. Isoflurane vs propofol (B); isoflurane vs control (C); propofol vs control (D). (Study IV)

Occasional second-degree AV-blocks were detected in dogs 4 and 6 five minutes after administration of iv medetomidine 40 µg/kg and dexmedetomidine 20 µg/kg. Frequent first-degree AV-blocks were seen in some dogs along with accentuated sinus arrhythmia and sinus pauses in all dogs after iv medetomidine or dexmedetomidine (I). After administration of iv dexmedetomidine 10 µg/kg, frequent episodes of first-degree AV-block were detected in all dogs during the next hour, and in dogs 2 and 6 a few episodes of second-degree AV-blocks were also detected (II). In Study III, dog 4 had frequent episodes of second-degree AV-blocks after administration of medetomidine 40 µg/kg and soon after propofol induction, and dog 6 had occasional blocks after dexmedetomidine 2 µg/kg. First-degree AV-blocks were frequently detected after premedication and during anaesthesia when dogs were treated at the medetomidine 40 µg/kg /dexmedetomidine 20 µg/kg and medetomidine 4 µg/kg /dexmedetomidine 2 µg/kg dose levels and occasionally after premedication at the medetomidine 0.4 µg/kg /dexmedetomidine 0.2 µg/kg dose level. In most Holter recordings, no VPCs were detected, the maximum frequency being two VPCs over 24 hours. VPCs were not seen during anaesthesia or during the recovery period and only twice during sedation. The development of second-degree AV-blocks varied from dog to dog and were seen most frequently in dog 4, moderately in dogs 2 and 6 and only rarely in the other dogs. The longest sinus pauses were 2.5 to 5.2 seconds long. Most of the heart blocks were seen during the premedication period, when bradycardia was most prominent. During the night after drug administration heart rate was similar between treatments and did not differ from that seen in baseline recordings (V).

5.2.2 Respiratory effects of medetomidine and dexmedetomidine (I-IV)

Respiratory rate and blood gas parameters were similar between medetomidine and dexmedetomidine, and in conscious dogs they were not affected by the dose (I-III). In general, respiratory rate, blood pHa and p_aO_2 decreased slightly (I, II) with no change (I) or some increase (II) in p_aCO_2. During anaesthesia, pHa decreased more when dogs were premedicated with iv medetomidine 40 µg/kg or dexmedetomidine 20 µg/kg than with the lower premedicant dose levels, but p_aCO_2 did not differ between treatments (III). In Study IV, respiratory acidosis was induced by both anaesthesia methods after im dexmedetomidine premedication, but p_aCO_2 was higher in the propofol group than in the propofol/isoflurane group during anaesthesia and the first hour of recovery.

5.2.3 Cardiorespiratory effects of levomedetomidine (I, II)

Levomedetomidine 10 and 20 µg/kg iv had no effect on cardiovascular parameters (I). In Study II, heart rate was lower with the infusion of the high dose of levomedetomidine than with the low dose of levomedetomidine or the placebo treatment both before and after dexmedetomidine administration. Diastolic blood pressure was higher with the high dose of levomedetomidine than with the other treatments before dexmedetomidine (Figure 10). Treatment with levomedetomidine caused no ECG abnormalities (I, II). Levomedetomidine with or without dexmedetomidine had no effect on respiratory parameters (I, II).

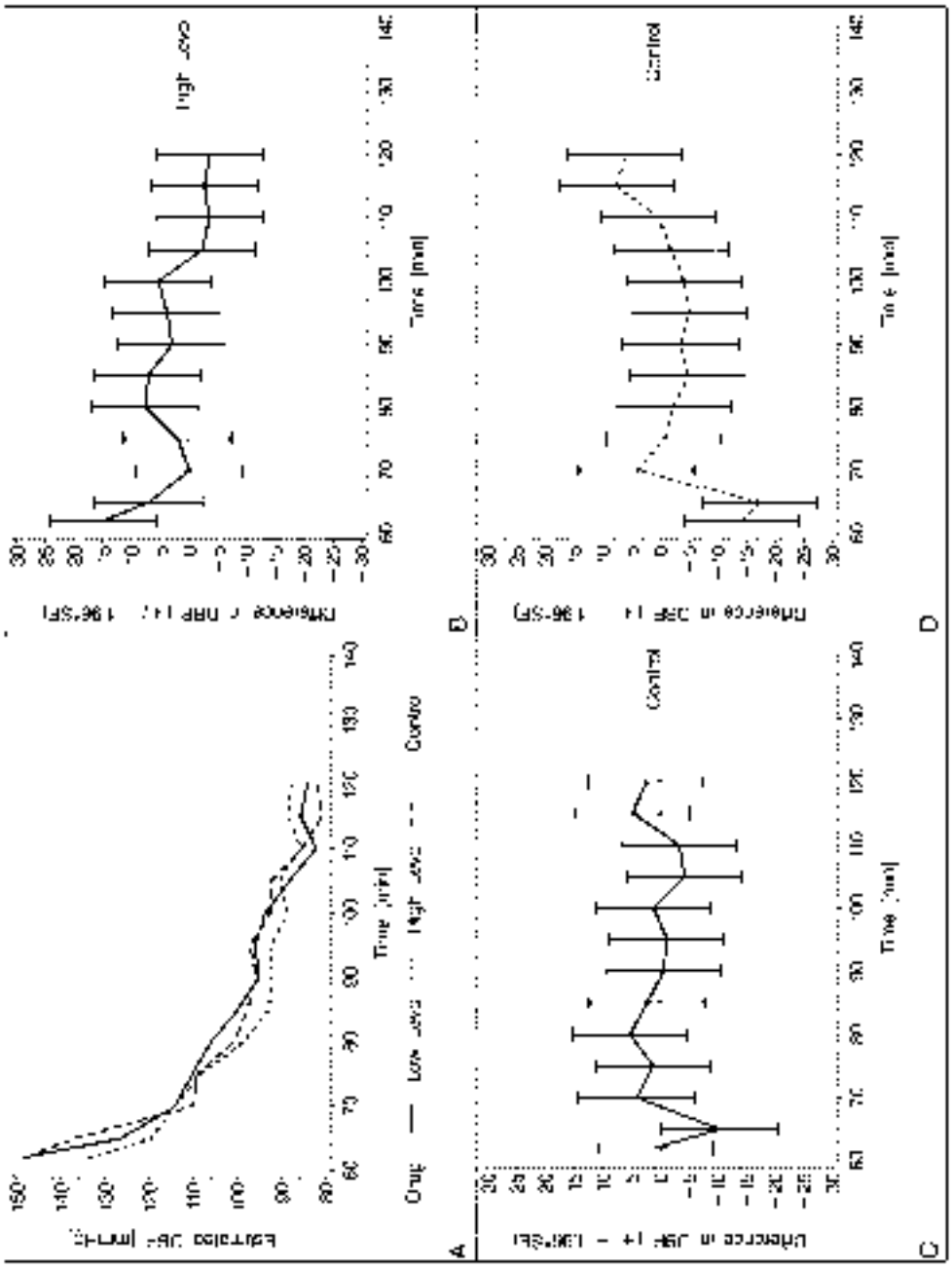

Figure 10
Estimated diastolic blood pressure (DBP) (A) and estimated difference with 95% CI between levomedetomidine 25 µg/kg/h (Low Levo) and levomedetomidine 200 µg/kg/h (High Levo) (B); between levomedetomidine 25 µg/kg/h and saline (Control) (C); between levomedetomidine 200 µg/kg/h and saline (D) in six dogs. The dogs received dexmedetomidine 10 µg/kg iv at 60 minutes. (Study II)

5.3 Pharmacokinetics and plasma drug concentrations (I, II)

The mean plasma concentrations for medetomidine, dexmedetomidine and levomedetomidine after a single iv dose are presented in figure 11. Clearance was higher and the volume of distribution at steady-state larger with iv levomedetomidine than with iv dexmedetomidine or racemic medetomidine, but the terminal half-lives did not differ between the drugs. Peak sedative and analgesic effects were observed at mean (± SD) plasma concentrations of 18.5 ± 4.7 ng/ml for medetomidine 40 µg/kg, 4.0 ± 4.5 ng/ml for dexmedetomidine 20 µg/kg and 5.5 ± 1.3 ng/ml for dexmedetomidine 10 µg/kg after iv bolus administration. The dogs were still moderately sedated at plasma concentrations of 9.5 ± 2.5 ng/ml for medetomidine 40 µg/kg, 6.2 ± 0.9 ng/ml for dexmedetomidine 20 µg/kg and 2.7 ± 0.9 ng/ml for dexmedetomidine 10 µg/kg (I).

Administration of iv bolus dexmedetomidine 10 µg/kg to the dogs receiving levomedetomidine infusion resulted in an abrupt increase in the combined levomedetomidine-dexmedetomidine concentration, which did not decrease during the subsequent hour (II).

5.4 Stress hormones (II, IV)

Levomedetomidine did not have a consistent influence on plasma catecholamine concentrations. After dexmedetomidine administration, the plasma adrenaline and noradrenaline concentrations decreased (II). Propofol-isoflurane or propofol infusion anaesthesia had no influence on plasma beta-endorphin, cortisol and noradrenaline concentrations at the end of anaesthesia and during recovery in dexmedetomidine-premedicated dogs. Adrenaline concentration increased more slowly during recovery when the dogs had received propofol infusion as compared with dexmedetomidine sedation (IV). Baseline plasma beta-endorphin concentration was 13.3 ± 2.3 pmol/l.

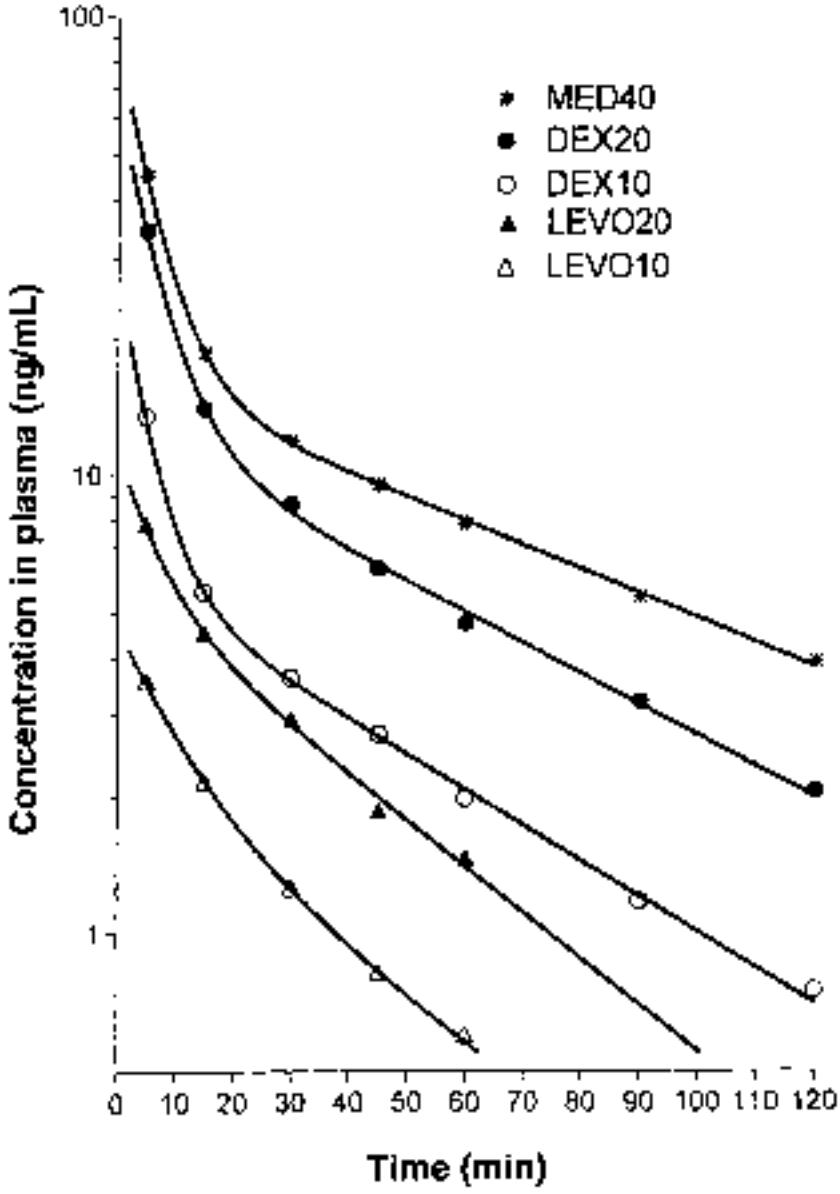

Figure 11
Mean plasma concentration of medetomidine (Med) 40 µg/kg; dexmedetomidine (Dex) 20 and 10 µg/kg; levomedetomidine (Levo) 20 and 10 µg/kg after iv bolus administration in six dogs. (Study I)

6. DISCUSSION

6.1 Methodological considerations

6.1.1 Statistical and study design considerations

Six experimental beagles were used in all of the trials. The beagles were purposefully bred, had the same background, age and breed and were kept in uniform housing and handling conditions. As the studies were non-clinical, the common statistical methods of experimental trials instead of power analysis were applied. Randomized 6 x 6 Latin square designs were utilized to diminish variation caused by the treatment order and variation between individuals. Accordingly, the sample size resulted in a primary outcome where significant differences between treatments were detected.

95% confidence intervals were calculated for the differences at each time-point to re-evaluate the power of the statistics used in some of the tests where significant differences were not shown. This assessment suggested that use of a larger sample size (either more beagles or more repetitions on the present dogs) might have revealed differences that here went undetected. Clinically significant differences could not be excluded in some of the variables showing no statistical significance.

The main investigator was unaware of whether dogs were receiving medetomidine or dexmedetomidine, thus filling the criteria of blinding. However, in Study III, the dose level could not be blinded, as the differences between the clinical effects of these doses were too distinct. Moreover, in Study IV, there was no blinding between isoflurane and propofol anaesthesia due to technical difficulties at the time of the study. The lack of blinding might have affected the assessment of the level of anaesthesia.

As haemodynamic parameters were used to evaluate the level of anaesthesia in Study III, the lack of haemodynamic response when the highest premedication dose levels were used may have caused a lower level of anaesthesia at this dose. The lack of a placebo group makes it difficult to evaluate whether the lowest premedication dose level had any clinical effects during anaesthesia. In Studies IV and V, we used dexmedetomidine alone as a control group to evaluate the effects of anaesthesia on clinical signs and recovery in dexmedetomidine-premedicated dogs. The use of a placebo group would have yielded a different aspect in this study.

In Study I, the pharmacokinetic results of iv medetomidine, dexmedetomidine and levomedetomidine would have been more accurate had there been supplementary sampling points, especially immediately after drug delivery. As the evaluation of the clinical effects of drugs was our priority, blood sampling was kept to a minimum.

6.1.2 Assessment of analgesia and the level of anaesthesia

We evaluated analgesia by studying flexor reflexes. In addition, the cold pressor test was used. We wanted to apply methods that are easy to use and repeat and that avoid tissue destruction or sensitization (wind-up) after numerous repetitions.

As pain behaviour consists of a pain sensation as well as a subjective reaction to pain (i.e. suffering), it is beyond our available methodologies to objectively evaluate how animals experience pain. In the absence of precise tools, we are forced to use methods such as withdrawal reflex observation, even though it is a somewhat inaccurate method for

measuring the analgesic effect of a drug. Because flexing of the leg in response to pinching is a spinal reflex, it does not testify that the animal has had a central experience of pain. However, in humans, a close correspondence exists between nociceptive withdrawal thresholds and subjective pain sensation (Page & France, 1997). The same observation is anecdotally assumed to be applicable to veterinary patients.

Withdrawal reflex tests are generally considered valid when α_2-adrenoceptor agonist-mediated analgesia is evaluated (Poree et al., 1998; Guo et al., 1999), as the analgesic action of dexmedetomidine is known to mainly be spinally mediated (Kalso et al., 1991; Hayashi et al., 1995b). It has been shown to interrupt the nociceptive pathway from the dorsal horn of the spinal cord to the ventral root, thus reducing the spinal reflex (Kendig et al., 1991; Savola et al., 1991b). At low doses of dexmedetomidine, a supraspinal mechanism may predominate (Pertovaara et al., 1991), reducing the unpleasantness of pain but with less impact on pain threshold (Jaakola et al., 1991; Kauppila et al., 1991). Supraspinal effects may also modulate the nociceptive flexor reflex threshold (Willer et al., 1979). As the analgesic action of dexmedetomidine is accompanied by sedation, the degree of sedation has an impact on the spinal reflexes and disturbs the assessment of pain.

The anaesthetic-sparing effect of a drug is usually studied by MAC determination using a supramaximal stimulus and observation of gross purposeful movements. In Study III, the anaesthesia level was defined by clinical signs and abolishment of the flexor reflex. In rats, depression of withdrawal force correlated well with MAC determination, being abolished at periMAC concentrations (Antunes et al., 2003; Jinks et al., 2003). However, MAC determinations should be done to assess possible difference in the anaesthetic-sparing effect between dexmedetomidine and medetomidine. In Study IV, common clinical signs were used to define the anaesthesia level between the two different anaesthesia methods. Adding a noxious stimulus, such as a tail clamp, might have helped to evaluate the level of anaesthesia more accurately.

6.2 Clinical signs of sedation and analgesia

The analgesic effect of dexmedetomidine was longer lasting than that of a corresponding dose of medetomidine, and a high dose of levomedetomidine reduced the sedative and analgesic effects of dexmedetomidine. The levo-enantiomer may have some interaction with the dextro-form, perhaps causing antagonism, competition at the same receptor sites or levomedetomidine action on α_1-adrenergic receptors. The α_2- to α_1-adrenoceptor selectivity ratio of levomedetomidine is much lower than that of dexmedetomidine (Aantaa et al., 1993), and levomedetomidine has been reported to be able to bind to and activate α_1-adrenergic receptors (Schwinn et al, 1991). α_1-adrenergic receptors can mediate behavioural activation in states of CNS depression (Pichler & Kobinker, 1985), and activation of central α_1-adrenergic receptors have been suggested to functionally antagonize the hypnotic responses to α_2- adrenoceptor agonists (Doze et al., 1989b; Guo et al., 1991). Jansson et al. (1998) speculated that levomedetomidine could transduce both agonistic and antagonistic signals through α_{2A}-adrenergic receptors. It may act as a weak partial α_2-adrenergic agonist in systems with low receptor activity. When the receptors express high activity, it behaves as an inverse α_2-adrenergic agonist (negative antagonist) similar to atipamezole by causing the opposite biological effect to dexmedetomidine (Jansson et al, 1998). Dexmedetomidine changes the balance between active and inactive receptors. Thus, the antagonizing property of levomedetomidine may become apparent, as it did in Studies I and II, suggesting that the use of dexmedetomidine is preferable to medetomidine in dogs.

The similarity of the level of sedation caused by different doses of dexmedetomidine (despite differing concentrations in plasma) in Study I suggests a ceiling effect exists that cannot be surpassed by increasing the dose. Schwinn et al., (1991) recommended avoiding high doses of dexmedetomidine, as dexmedetomidine's ability to activate α_1-adrenergic receptors may attenuate its α_2-mediated hypnotic action. In cats, increasing the blood concentration of dexmedetomidine beyond a certain level decreased the level of sedation, even though the level of analgesia increased (Ansah et al., 2000). Likewise, rats showed signs of excitement or decreased sedation after a very high dose of dexmedetomidine (Doze et al., 1989a; Savola & Virtanen, 1991). In the present study, these signs were not seen when the highest doses (20 µg/kg of iv dexmedetomidine and 40 µg/kg of iv medetomidine) were used. However, our results suggest that these doses may be unnecessarily high for sedation in dogs, as increasing the dose above 10 µg/kg of iv dexmedetomidine did not increase the level of sedation or analgesia; it merely resulted in longer lasting effects.

The cold pressor test, a method developed to assess sympathetic nervous system activity, has been used to evaluate the analgesic effect of α_2-adrenergic agonist drugs in humans (Ebert et al., 2000; Hall et al., 2000). Pain sensation to the test was decreased even at low concentrations of dexmedetomidine, and at higher doses the deeper plane of sedation resulted in no pain response (Ebert et al., 2000). The usefulness of the cold pressor test in dogs was investigated in Study IV, but the dose of dexmedetomidine (10 µg/kg) was apparently too high in this group of dogs. While most dogs showed minimal or no response to cold water after dexmedetomidine, one dog resisted the test vigorously every time. An increase in respiratory rate was generally a more sensitive parameter than changes in cardiovascular variables for revealing production of sympathetic activity. The cold pressor test might be more useful with lower doses of dexmedetomidine; however, in less sedated dogs, a learning effect might modify physical response after repeated stimulus.

Signs of light analgesia were already seen after 2 µg/kg of iv dexmedetomidine. Muir et al. (1999) observed a lack of analgesic effect (measured by the clinical signs of pain) with im medetomidine at doses of 2 and 5 µg/kg in dogs of various breeds. In our study, the moderate sedation accompanied with the signs of light analgesia may have affected the observable pain response.

Our results suggest that dexmedetomidine could be more useful than medetomidine as an analgesic in dogs, and the analgesic effects of iv dexmedetomidine are observable at doses above 2 µg/kg.

6.3 Effects of premedicants on anaesthesia and recovery profile

Dexmedetomidine and medetomidine reduced the requirements of propofol and isoflurane dose-dependently to reach similar planes of anaesthesia. Combined mean end-tidal isoflurane concentration for all dose levels was transiently lower after dexmedetomidine than after medetomidine, and this finding could be attributable to the prolonged analgesic effect of dexmedetomidine. Less selective α_2-adrenergic agonist drugs are claimed to reduce anaesthetic requirements less than dexmedetomidine, probably due to increased α_1-adrenoceptor stimulation (Hayashi & Maze, 1993). In sheep undergoing orthopaedic surgery, dexmedetomidine had similar effects on isoflurane requirements as comparable doses of medetomidine (Kästner et al., 2001a; Kästner et al., 2001b). Although our results suggest that the presence of the levo-enantiomer may influence the anaesthetic-sparing

effect of dexmedetomidine, a larger sample size is needed to prove this assumption.

The optimal dose level of iv dexmedetomidine as a premedicant was 2 µg/kg, as intense bradycardia and hypotension were avoided during propofol/isoflurane anaesthesia after this dose (III). However, the effect was short-lasting and the sedation achieved by this dose may not consistently be adequate for healthy dogs. While the premedicants were administered iv in Study III, the im route seems to be preferable to avoid abrupt cardiovascular changes and to lengthen the sedative and analgesic effects of the α_2-adrenergic agonist drug. The optimal im premedicant medetomidine dose in dogs has been suggested to be 20 µg/kg (Young et al., 1990), or between 10 and 40 µg/kg, with the lower dose causing inconsistent and the larger dose excessive sedation for preoperative purposes (Räihä et al., 1989). Muir et al. (1999) reported that im doses of medetomidine at or below 5 µg/kg caused excitement in some dogs of various breeds. However, in the present study, no signs of excitement were observed in the beagles treated iv with either 4 µg/kg of medetomidine or the equipotent dexmedetomidine dose (2 µg/kg). The discrepant results might be explained by differences in administration methods or by only laboratory beagles being used in our study. When determining the premedicant dose of an α_2-adrenergic agonist drug, the size, age, general behaviour and health status of the dog should be taken into account to achieve the optimal dose for each patient.

The effects of α_2-adrenergic agonist drugs might reduce the sensitivity of haemodynamic variables as signs of anaesthetic depth (Erkola et al., 1994), which was demonstrated with the use of different iv dexmedetomidine and medetomidine premedicant dose levels in Study III. At the lowest premedicant dose level, distinct haemodynamic responses occurred to noxious stimulus during anaesthesia. At higher premedicant doses, these changes were rarely seen, although decreasing the dose of isoflurane resulted in signs of awakening (movement) after pinching. Schmeling et al. (1999) reported that after dexmedetomidine both haemodynamic and spinal movement responses are more attenuated than those of the higher brain functions, such as those detected by electroencephalogram.

In humans, similar (Lawrence & DeLange 1997) or even faster (Jaakola et al., 1992) recoveries after premedication with dexmedetomidine as compared with placebo have been described. In our studies the recoveries were delayed after high premedicant doses. In Study IV, propofol/isoflurane anaesthesia had no additional effect on recovery while it was delayed after propofol infusion. Contradictory, the recovery profile in humans after propofol infusion has been similar to that after isoflurane anaesthesia when α_2-agonist premedicants have not been used (Myles et al., 2000; Godet et al., 2001), and a rapid recovery after propofol infusion is reported in dogs (Nolan & Reid, 1993). Cardiovascular effects of dexmedetomidine and pharmacokinetic interactions may have altered the rate of metabolism of both dexmedetomidine and propofol (Mouton Perry et al., 1991; Bührer et al., 1994). In humans, a low dose of dexmedetomidine reduced the propofol infusion dose but did not affect the pharmacokinetics of propofol or recovery time after infusion (Dutta et al., 2001). In dogs, blood systemic clearance of propofol was almost halved by premedication with 20 µg/kg medetomidine (Hall et al., 1997). Dexmedetomidine and levomedetomidine have been shown to be potent inhibitors of drug-metabolizing activities in vitro (Pelkonen et al., 1991; Kharasch et al., 1991, 1992), but less potent in vivo (Pelkonen et al., 1991). While the hexobarbital sleeping time in rats was prolonged by a high dose of levomedetomidine, a clinical dose had no effect (Pelkonen et al., 1991). Dexmedetomidine is considered to have a low potency for inhibiting P450 enzyme function in dogs (Maze et al., 1991). However, Kharasch et al. (1992) suggested that

dexmedetomidine might be less susceptible to drug interactions than the racemic mixture, and thus, preferable as a premedicant. In the present study, the recovery profile after propofol/isoflurane anaesthesia was unaffected by the premedicant drug, suggesting that medetomidine and dexmedetomidine are equally useful as premedicants as far as uneventfulness of recovery is concerned. The effects of medetomidine and dexmedetomidine on recovery after propofol infusion were not compared in this study.

6.4 Cardiorespiratory effects

The cardiorespiratory effects of dexmedetomidine were similar to the equipotent doses of medetomidine (I, III). However, a high dose of levomedetomidine decreased heart rate, increased blood pressure and, when combined with dexmedetomidine, enhanced bradycardia (II). Accordingly, it could be speculated that the presence of high concentrations of circulating levomedetomidine molecules has a clinically unfavourable effect. The weak partial α_2-adrenergic action of levomedetomidine (Jansson et al., 1994), α_1-adrenergic activation induced vasoconstriction, or both, may explain these findings. The bradycardic effects of medetomidine and dexmedetomidine have also been compared in sheep and rats, and the results suggest that medetomidine may lower heart rate more than dexmedetomidine. Intraoperative heart rate was lower in sheep premedicated with medetomidine than in those premedicated with an equipotent dose of dexmedetomidine, although the isoflurane requirement did not differ (Kästner et al., 2001b). In rats, a half-maximal bradycardic effect was obtained at a dose of 0.4 µg/kg of medetomidine, while a dose of 0.5 µg/kg of dexmedetomidine was required to reach a similar effect (Savola & Virtanen, 1991). In Study III, overall heart rate was higher with the middle dose of medetomidine than with the corresponding dose of dexmedetomidine during isoflurane anaesthesia. This could be due to anaesthetic-induced changes, as isoflurane concentration tended to be higher with medetomidine 4 µg/kg than with dexmedetomidine 2 µg/kg.

The additional cardiovascular effects of the small doses of anaesthetic drugs were minimal when compared to the highest doses of medetomidine or dexmedetomidine alone. When blood level of dexmedetomidine is sufficiently high, peripheral α_{2B}-adrenoceptors are activated, causing vasoconstriction and consequently blood pressure increases (Link et al., 1996). The vasoconstrictive and sympatholytic effects of a high dose of dexmedetomidine may predominate and counteract the vasodilatation caused by isoflurane, thus inducing bradycardia and preventing hypotension during anaesthesia (Bloor et al., 1992b). Bloor et al. (1992b) have suggested that the vasoconstrictive effect of an α_2-adrenoceptor agonist drug might be more prominent and longer lasting in dogs than in humans. Moreover, as the doses of dexmedetomidine administered to humans are usually much smaller than those given to dogs, the predominant effect of dexmedetomidine in humans is a centrally mediated decrease in blood pressure, while in dogs initial hypertension is more commonly seen.

In awake humans blood pressure has been shown to decrease at a plasma dexmedetomidine concentration below 1.2 ng/ml, which was achieved by iv infusion of the drug (Ebert et al., 2000). In Study I, diastolic blood pressure had decreased to normal levels at plasma dexmedetomidine concentrations of 4 to 9 ng/ml, but the dogs were still not hypotensive at a dexmedetomidine concentration of approximately 1 ng/ml two hours after drug administration. Similarly, after receiving im dexmedetomidine 10 µg/kg, blood pressure stayed within reference range during the three-hour recovery despite continuing bradycardia (IV). However, when the lowest iv premedicant doses (medetomidine 0.4 µg/kg

and dexmedetomidine 0.2 µg/kg) were used before propofol/isoflurane anaesthesia (III), the dogs were more hypotensive than usually reported under a light level of isoflurane anaesthesia only (Klide, 1976; Mutoh et al., 1997). The induction dose of propofol may have decreased blood pressure further, but this result can also suggest that at these low premedicant doses central effects of dexmedetomidine predominated over peripheral effects. Hypotensive effects have been reported to exceed the vasoconstrictive effects at bolus iv doses below 1 µg/kg of dexmedetomidine in anaesthetized dogs (Lawrence et al., 1996b). In the current study, premedication with iv 2 µg/kg of dexmedetomidine or iv 4 µg/kg of medetomidine before propofol/isoflurane anaesthesia resulted in the most stable cardiovascular effects when compared with the higher and lower dose levels.

In dogs, propofol is claimed to maintain arterial blood pressure better than isoflurane (Keegan & Greene, 1993; Deryck et al., 1996) with a similar (Deryck et al., 1996) or lower (Keegan & Greene, 1993) heart rate. When medetomidine is combined with propofol infusion, variable cardiovascular effects have been reported (Vainio, 1991; Lagerweij et al., 1993; Hammond & England, 1994; Hall et al., 1997). In Study IV, blood pressure was similar for propofol infusion and controls (dexmedetomidine only), which implies that the vasoconstrictive effects of dexmedetomidine predominated and prevented hypotension. Blood pressure stayed within normal reference range even during isoflurane, although the dogs were not surgically stimulated. Even though blood pressure was similar, heart rate was consistently higher during propofol infusion compared with dexmedetomidine at the same time. This finding may at least partially be explained by the hypercapnia induced by propofol (Taylor, 1998; Mas et al., 2000).

No differences were present between medetomidine and dexmedetomidine in ECG findings, and levomedetomidine showed no effects on heart rhythm. VPCs were not detected in intermittent ECG recordings or in most Holter recordings, but the low number of dogs used may partly explain the lack of findings. In healthy non-anaesthetized dogs, VPCs do exist but are found infrequently (Hall et al., 1991; Ulloa et al., 1995; Meurs et al., 2001). In a Holter study of 228 healthy beagles, 49 showed ventricular ectopy, most having less than nine single VPCs over a 24-hour period (Ulloa et al., 1995). In the same study, second-degree AV-blocks were sporadically encountered. In severely diseased canine patients undergoing splenectomy, a high incidence of perioperative VPC and ventricular tachycardia was revealed by Holter analysis (Marino et al., 1994). In a study of 50 canine patients free of cardiac diseases, VPCs and atrioventricular conduction defects were the most frequently observed arrhythmias during the recovery period. Acepromazine, pethidine and halothane were the drugs most commonly included in the anaesthetic regimen in this earlier study, and the type of surgical or diagnostic procedure did not influence the incidence of arrhythmias (Buss et al., 1982). Reports on the effects of α_2-adrenoceptor agonists on ventricular arrhythmias are inconsistent. The stimulation of α_1-adrenoceptors may cause ventricular arrhythmias (Hayashi et al., 1988) and xylazine, a less α_2-specific drug than dexmedetomidine, has been reported to decrease the arrhythmogenic dose of adrenaline in anaesthetized dogs (Tranquilli et al., 1986, 1988). In later studies, however, xylazine or medetomidine did not enhance arrhythmogenicity in either halothane- (Lemke et al., 1993; Pettifer et al., 1996) or isoflurane-anaesthetized dogs (Lemke et al., 1993). Dexmedetomidine has been shown to prevent adrenaline-induced arrhythmias in halothane-anaesthetized dogs (Hayashi et al., 1991). Hayashi et al. (1993) and Kamibayashi et al. (1995b) have suggested that this effect is due to the action of dexmedetomidine on imidazoline-preferring receptors in the CNS. Dexmedetomidine has been demonstrated to reduce the oxygen deficiency of the ischaemic myocardium in anaesthetized dogs

(Roekaerts et al., 1996). In human patients undergoing vascular surgery, dexmedetomidine administration reduced the haemodynamic responses to perioperative stress (Talke et al., 1995). The low frequency of VPCs detected in Study V is in accordance with these earlier reports.

The occurrence of AV-blocks was dose-dependent, variable between dogs and no differences could be shown between dexmedetomidine and medetomidine. The AV-blocks were mostly seen soon after administration of the drugs, when bradycardia was most prominent. During anaesthesia the AV-blocks decreased or vanished as heart rate increased, but they sometimes reappeared during the early recovery period. The length of sinus pauses during treatments was similar to that reported earlier in non-anaesthetized dogs (Hall et al., 1991), and the pauses coincided with bradycardia. The AV-blocks and sinus pauses detected during these studies were not considered to be clinically significant.

The respiratory parameters stayed within normal physiological values even during profound sedation, and levomedetomidine had no respiratory effects alone or combined with dexmedetomidine (I, II). During anaesthesia hypoventilation was seen (III, IV). The degree of hypercapnia was similar between medetomidine and dexmedetomidine and independent of the premedicant dose, contradictory to some previous studies in dogs. Nguyen et al. (1992) have reported signs of improved ventilation after very high dexmedetomidine doses. Combination of dexmedetomidine and isoflurane has resulted in less respiratory depression than isoflurane alone (Bloor et al., 1989; Nguyen et al., 1992). However, the present results suggest that increasing the premedicant dose may not offer any respiratory benefit even though the delivery of isoflurane can be decreased (III). Dexmedetomidine combined with propofol infusion resulted in more profound hypoventilation and respiratory acidosis than dexmedetomidine and propofol/isoflurane (IV). In earlier propofol infusion studies, dogs were either ventilated to normocapnia (Keegan & Greene, 1993) or breathed room air, showing only moderate increases in p_aCO_2 with occasional hypoxemia (Vainio, 1991; Hall et al., 1997). Hyperoxia has been reported to impair ventilation (Gaudy et al., 1988), and the delivery of pure oxygen may partly explain the more severe respiratory depression shown earlier. As the dogs with the highest p_aCO_2 values showed signs of light anaesthesia, the hypoventilation may have been overlooked if end-tidal CO_2 had not been monitored. Thus, isoflurane may be a safer choice than propofol as an anaesthetic in dexmedetomidine-premedicated, spontaneously ventilating dogs.

In Study III, the combination of iv medetomidine 40 µg/kg or dexmedetomidine 20 µg/kg with propofol/isoflurane induced slight metabolic acidosis. Impaired tissue perfusion may explain this finding, despite saturation of arterial haemoglobin being adequate. However, arterial lactate concentrations were unchanged after iv dexmedetomidine 10 µg/kg in dogs (Lawrence et al., 1996a), and likewise in Study IV blood lactate values after 10 µg/kg of dexmedetomidine were within the reference range reported for healthy conscious dogs (Hughes et al., 1999). The lower lactate values detected during propofol infusion than during propofol/isoflurane anaesthesia suggests better tissue perfusion with propofol, which might be caused by the more severe hypercapnia in this group (IV).

While these studies showed no clinically significant cardiorespiratory differences between medetomidine and dexmedetomidine, the latter may be more suitable in dogs due to the bradycardic effects of levomedetomidine. When dexmedetomidine is used as a premedicant, a dose level of 2 µg/kg is suggested to achieve stable cardiovascular effects, and maintenance of anaesthesia with isoflurane may depress ventilation less than propofol.

6.5 Pharmacokinetics

Medetomidine is metabolized mainly by hepatic hydroxylation in dogs (Salonen, 1992), while in humans hepatic glucuronidation of dexmedetomidine and levomedetomidine is more efficient than in dogs. In dog liver microsomes, glucuronidation of levomedetomidine was eight times more efficient than that of dexmedetomidine (Kaivosaari et al., 2002). In Study I, clearance of levomedetomidine was more rapid than that of dexmedetomidine or medetomidine, This could be caused by partly divergent metabolic pathways for these enantiomers. Furthermore, dexmedetomidine may reduce its own elimination rate dose-dependently via its haemodynamic effects (Salonen et al., 1995). In humans, the decrease in cardiac output with increasing plasma concentrations of dexmedetomidine resulted in a corresponding decrease in dexmedetomidine elimination clearance (Dutta et al., 2000). The circulatory effects of dexmedetomidine probably also account for the larger distribution volume with levomedetomidine than with dexmedetomidine and medetomidine in Study I. Dexmedetomidine has been shown to modify thiopental body disposition in a similar way (Bührer et al., 1994). The haemodynamic effects of dexmedetomidine most likely explain the high combined plasma levomedetomidine and dexmedetomidine concentrations during infusion of levomedetomidine in Study II. Accordingly, when high doses of medetomidine are used, the plasma levomedetomidine concentration and even the clinical effect of levomedetomidine may be unexpectedly elevated.

6.6 Stress hormones

Medetomidine has been demonstrated to control the stress response induced by anaesthesia and surgery during the perioperative period in dogs (Benson et al., 2000; Ko et al., 2000; Väisänen et al., 2002). In Study IV, while recovery was faster after isoflurane than after propofol infusion, no signs of excitation or anxiety were seen, and the endocrine stress response was mild and similar between treatments. Dexmedetomidine apparently concealed possible stress effects of anaesthesia during recovery. The delayed increase in adrenaline concentration after propofol infusion is most likely due to the slower recovery in this group, when compared with the other treatments. The baseline beta-endorphin level in these dogs was comparable with the concentration detected after dexmedetomidine premedication and was shown to be unaffected by propofol or propofol/isoflurane anaesthesia (IV). In humans, a low level of beta-endorphin is considered a sign of stress-free anaesthesia (Lehtinen et al., 1984). In horses, anaesthesia alone and especially hypoxic anaesthesia has been revealed to increase plasma beta-endorphin levels (Taylor et al., 2000). In dogs undergoing ovariohysterectomy, while the concentration of beta-endorphin increased during surgery, it was similar in dogs receiving either medetomidine/opioid or acepromazine/opioid premedication (Väisänen et al., 2002). In our studies, medetomidine and dexmedetomidine had similar effects on stress response in dogs, and anaesthesia did not modify the effect.

7. CONCLUSIONS

Dexmedetomidine was at least as safe and effective as the corresponding dose of medetomidine as a sedative, analgesic and premedicant in laboratory beagles. The pharmacokinetics of dexmedetomidine and racemic medetomidine were similar, but clearance of levomedetomidine was more rapid than that of the other drugs. Levomedetomidine did not cause any observable behavioural effects in conscious dogs. However, it did reduce the sedative and analgesic effects of dexmedetomidine and intensified bradycardia, suggesting that use of dexmedetomidine might be preferable to medetomidine in dogs. The dose level of 2 µg/kg of dexmedetomidine resulted in most stable cardiovascular effects when used as a premedication before propofol/isoflurane anaesthesia. After dexmedetomidine premedication, propofol/isoflurane anaesthesia was considered more suitable than propofol infusion due to a milder degree of respiratory depression and faster recovery. The cold pressor test produced variable responses among the dogs and was not a reliable stress stimulus with the dexmedetomidine dose used. In beagles treated with dexmedetomidine alone or combined with propofol infusion or propofol/isoflurane, ventricular arrhythmias were detected no more frequently than in healthy non-anaesthetized dogs.

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