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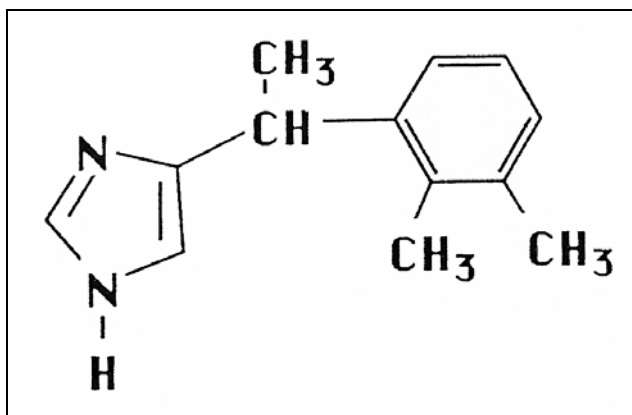
**USE OF THE ALPHA-2-ADRENOCEPTOR AGONISTS  
MEDETOMIDINE AND DEXMEDETOMIDINE  
IN THE SEDATION AND ANALGESIA OF  
DOMESTIC CATS**

Osei Bonsu Ansah

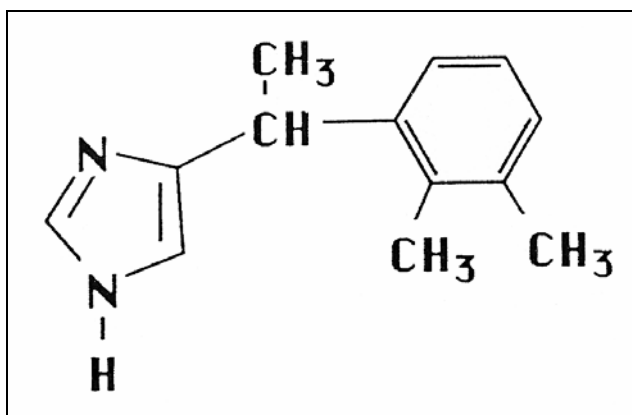
ACADEMIC DISSERTATION

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in the Auditorium Maximum, Hämeentie 57, 00580 Helsinki,  
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HELSINKI 2004



*Dedicated to*  
*my dear mother **Susanna Abena Amoa Owusu-Ansah***  
*and late father **Abraham Akwasi Owusu-Ansah***  
*for all the sacrifices you made,*  
*for working hard to send me to school,*  
*for love and care, and for being there*  
*when I most needed you.*



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## 1. ABSTRACT

The racemate medetomidine (MED), an alpha-2-adrenoceptor agonist, and its dextro-rotatory optical isomer dexmedetomidine (DEX) were studied in cats. The sedative effect of oral-mucosal application of MED and selected pharmacokinetic variables were evaluated and compared with intramuscular (I.M.) administration of the same dose of drug (n = 7). Sedative and analgesic effects of MED were also studied at different dose levels following either I.M. administration (n = 6) or continuous intravenous (I.V.) step infusion in cats (n = 6) and further compared with sedation and analgesia induced by equivalent doses of DEX (half the dose of MED). The effectiveness of using MED for post-operative pain relief in cats (n = 64) that had undergone ovariohysterectomy was evaluated and compared with butorphanol. The relationship between plasma and cerebrospinal fluid (CSF) concentrations of MED and how these concentrations vary with the levels of sedation in experimental rabbits (n = 23) were studied with the assumption that similar relationships may exist in cats.

The results obtained indicated that oral-mucosal application of MED is effective for sedating cats and that when salivation and vomiting are minimal or absent, systemic drug availability and the extent of sedation are comparable between the oral-mucosal and I.M. routes. Maximum blood concentration of MED and clinical sedation are reached later with oral-mucosal application than with I.M. administration. Both MED and DEX induce dose-dependent sedation and analgesia in cats that reach ceiling doses, beyond which sedation may be reduced. DEX (at half the dose of MED) is as effective as MED for the sedation and analgesia of cats. The sedative and analgesic effects of MED in cats are mediated predominantly via its dextro-rotatory optical isomer. The levo-rotatory isomer in MED may introduce some inconsistencies to the therapeutic effects of the drug at high doses and make the effects of MED unpredictable in terms of dose variation. The presence of the l-isomer in MED may not always be of therapeutic disadvantage. Intramuscularly administered MED relieves post-operative pain in cats, but it is not as potent as butorphanol. Serum concentration of MED predicts the concentration of MED

in the CSF of rabbits. Increasing the concentration of MED in the CSF will not necessarily lead to an increase in the level of sedation.

## 2. LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, referred to in the text by their Roman numerals:

- I      Ansah O.B., Raekallio M. and Vainio O.  
Comparing oral and intramuscular administration of medetomidine in cats.  
J. Vet. Anaesth. 1998; **25**:41-46.
  
- II     Ansah O.B., Raekallio M. and Vainio O.  
Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration.  
J. Vet. Pharmacol. Therap. 1998; **21**:380-387.
  
- III    Ansah O.B., Raekallio M. and Vainio O.  
Correlation between serum concentrations following continuous intravenous infusion of dexmedetomidine or medetomidine in cats and their sedative and analgesic effects.  
J. Vet. Pharmacol. Therap. 2000; **23**:1-8.
  
- IV    Ansah O.B., Vainio O., Hellsten C. and Raekallio M.  
Postoperative pain control in cats: clinical trials with medetomidine and butorphanol.  
Vet. Surg. 2002; **31**:99-103.
  
- V      Raekallio M., Ansah O.B., Kuusela E. and Vainio O.  
Some factors influencing the level of clinical sedation induced by medetomidine in rabbits.  
J. Vet. Pharmacol. Therap. 2002; **25**:39-42.

### 3. ABBREVIATIONS

$\alpha_2$	alpha-2-adrenergic receptor (alpha-2-adrenoceptor)
$\alpha$ -agonist	alpha-adrenergic receptor (adrenoceptor) agonist
$\alpha$ - and $\beta$ - receptors	alpha- and beta-adrenergic receptors (adrenoceptors)
ADH	antidiuretic hormone
AUC-c	area under drug concentration-time curve
AUC-s	area under sedation-time curve
$\text{Ca}^{2+}$	calcium ion
cAMP	cyclic adenosine monophosphate
CNS	central nervous system
CSF	cerebrospinal fluid
DEX	dexmedetomidine
EDTA	ethylenediamine tetra-acetic acid
GIRK channel	G-protein-gated inwardly rectifying $\text{K}^+$ channel
G-protein	guanine nucleotide binding regulatory proteins
Hb	haemoglobin
$\text{H}_2\text{O}$	water
I.M.	intramuscular
I.P.	intraperitoneal
I.V.	intravenous
$\text{K}^+$	potassium ion
LC	locus caeruleus
LEV	levomedetomidine
LVOT	left ventricular outflow tract
MED	medetomidine
$\text{Na}^+$	sodium ion
$\text{N}_2\text{O}$	nitrous oxide
$\text{pCO}_2$	carbon dioxide tension
pH	logarithm of the reciprocal of hydrogen ion concentration
$\text{pO}_2$	oxygen tension
S.C.	subcutaneous

#### 4. INTRODUCTION

Recent advances made in alpha-2-adrenoceptor pharmacology suggest that agents acting on this receptor population may possess strong therapeutic potential in the development of anaesthesia. Several alpha-2-adrenoceptor agonists have therefore been manufactured for human or animal use. Medetomidine ( $\pm$  4-[1-(2, 3-dimethylphenyl)ethyl]-1 H-imidazole) is one such agonist that has garnered the attention of many small animal practitioners as a sedative-analgesic in recent years. Studies carried out with medetomidine in some animal species indicate that the pharmacological activity of the drug resides predominantly in its dextro-rotatory optical isomer (dexmedetomidine) (Segal et al., 1988; Virtanen et al., 1988; MacDonald et al., 1991; Savola and Virtanen, 1991; Kuusela et al., 2000; 2001b; Kastner et al., 2001a; 2001b). Medetomidine is more potent than an older, and widely used alpha-2-agonist xylazine (Virtanen et al., 1988). For sedative-analgesic purposes in cats, advantages of medetomidine over xylazine have been demonstrated (Verstegen et al., 1989; 1990; 1991a). Although medetomidine was discovered in the early 1980s (Karjalainen, 1981), relatively few studies with this drug or any of its isomers have been carried out in cats, compared with, for instance, dogs. Studying this drug and its isomers more intensively would be desirable to increase their usefulness in feline anaesthesia and to maximize overall therapeutic benefits in cats. Research into how medetomidine or dexmedetomidine can safely and effectively be delivered to cats in a simple non-invasive manner can, for example, provide clues on how cat owners could administer medetomidine (in a suitable form) to their pets in times of need. At some concentrations, the l-isomer in medetomidine induces weak alpha-2-agonistic (Savola and Virtanen, 1991) or alpha-2-antagonistic (MacDonald et al., 1991) effects in certain animal species. Both medetomidine (Virtanen et al., 1988) and dexmedetomidine (Schwinn et al., 1991) have also been shown to possess affinity (although very weak) for alpha-1-adrenoceptors. Therefore, for effective control and optimal use of medetomidine or dexmedetomidine in cats, it is essential to know how blood and cerebrospinal fluid (CSF) concentrations of these drugs correlate with their sedative, analgesic and other clinical effects. The pharmacological profiles of medetomidine and dexmedetomidine suggest that these drugs may possess some benefits

for the control of post-operative pain in cats. Since studies addressing the above-mentioned questions are currently either limited or lacking, further research with medetomidine or dexmedetomidine in cats is warranted.

## **5. REVIEW OF LITERATURE**

### **5.1. General classification of adrenergic receptors**

Adrenergic receptors (adrenoceptors) are membrane-bound receptors that are located on neuronal and non-neuronal tissues throughout the body, where they mediate different responses to the endogenous catecholamines adrenalin and noradrenaline and their analogues. Based on pharmacological studies in isolated tissues, Ahlquist (1948) first proposed that adrenoceptors be divided into two distinct classes, alpha- and beta- ( $\alpha$ - and  $\beta$ -) adrenoceptors. Both  $\alpha$ - and  $\beta$ -receptors were further subdivided based on different criteria.

### **5.2. Subclassification of alpha-adrenoceptors**

Langer (1974) subsequently proposed that the postsynaptically located  $\alpha$ -receptor mediating effector organ response be designated  $\alpha_1$  and that the presynaptically located inhibitory autoreceptor regulating neurotransmitter release be designated  $\alpha_2$ . Further studies revealed that the anatomical location alone was insufficient for classifying adrenoceptors (Schimmel, 1976; Berthelsen and Pettinger, 1977). Berthelsen and Pettinger (1977) therefore suggested a functional classification based on the type of function mediated by the receptor rather than its anatomical location. Accordingly, adrenergic receptors mediating inhibitory responses were designated  $\alpha_2$  and those mediating excitatory responses  $\alpha_1$ . Deficiencies in the functional mode of classification were also uncovered (Drew and Whiting, 1979). Thus, the anatomical and functional classifications gave way to a pharmacological classification based on the relative potencies and affinities of selective agonists and antagonists for these receptors.

### 5.3. Alpha-2-adrenoceptors

#### 5.3.1. *Alpha-2-adrenoceptor subtypes*

On the basis of radioligand binding profile, amino acid sequence and chromosomal location, four distinct  $\alpha_2$ -receptor subtypes –  $\alpha_{2A}$  (corresponding to  $\alpha_2$ -C10),  $\alpha_{2B}$  (corresponding to  $\alpha_2$ -C2),  $\alpha_{2C}$  (corresponding to  $\alpha_2$ -C4) and  $\alpha_{2D}$  – have been characterized (Bylund, 1985; Kobilka et al., 1987; Murphy and Bylund, 1988; Regan et al., 1988; Lomasney et al., 1990; Bylund et al., 1992; 1994; MacKinnon et al., 1994). The  $\alpha_{2D}$  subtype exhibits a distinct pharmacological profile but from sequence homology is believed to be a species variation of  $\alpha_{2A}$  ( $\alpha_{2A}$  occurs in humans, dogs, pigs and rabbits, whereas  $\alpha_{2D}$  occurs in rats, mice and cattle) and is not considered to be a separate entity (Simonneaux et al., 1991; Kurose et al., 1993; Bylund et al., 1994; 1995; Hieble et al., 1995; Docherty, 1998). This subtype is therefore designated as  $\alpha_{2A}$ ,  $\alpha_{2D}$  or  $\alpha_{2A/D}$  in different studies (Calzada and Artinano, 2001).

#### 5.3.2. *Alpha-2-adrenoceptor signal-transduction mechanisms*

In many cells,  $\alpha_2$ -receptors can simultaneously activate different signal-transduction systems (Jones et al., 1991). Each of the receptor subtypes is capable of coupling to multiple signal transduction pathways (Cotecchia et al., 1990). Generally, when an  $\alpha_2$ -receptor is activated, it interacts with a guanine nucleotide regulatory binding (G) protein. The activated G-protein then signals a second messenger system (an intracellular effector system) or modulates ion channel activity to trigger various physiological responses (for review, see Berkowitz and Schwinn, 1994). Activation of  $\alpha_2$ -receptor on the surface of most cells may predominantly lead to the inhibition of adenylate cyclase activity via coupling through membrane-linked pertussis toxin-sensitive inhibitory ( $G_{i/o}$ ) proteins. This causes a decrease in the production of cAMP in target cells (Limbird, 1988). All three adrenoceptor subtypes have been shown to inhibit activation of adenylate cyclase (Bylund, 1992). These receptors do, however, possess the potential to couple physically and functionally to inhibitory ( $G_i$ ) as well as stimulatory ( $G_s$ ) proteins (Eason et al., 1992;

Eason and Liggett, 1995). The  $\alpha_{2A/D}$  mediates inhibition or stimulation of adenylate cyclase activity at low or high concentrations of  $\alpha_2$ -agonist, respectively (Eason et al., 1992).

Eason and others (1992) have reported that all of the subtypes couple to  $G_i$ -proteins with similar efficiencies but couple to  $G_s$ -proteins with efficiencies of  $\alpha_{2A/D} > \alpha_{2C} > \alpha_{2B}$ . Pohjanoksa and others (1997) also reported that  $\alpha_{2B}$  is coupled to both  $G_i$  and  $G_s$  proteins, while the  $\alpha_{2A/D}$  and  $\alpha_{2C}$  couple to  $G_i$  and transduce only inhibition of adenylate cyclase activity. Another study, however, suggests that the  $\alpha_{2A/D}$  couples not only to  $G_i$  but also to  $G_s$  (Brink et al., 2000). Some of the reports on adrenoceptor subtype coupling to different G-proteins may seem contradictory, but different agonists were used in the various studies and  $\alpha_2$ -agonists have been shown to differ in their abilities to activate  $G_i$ -or  $G_s$ -proteins (Eason et al., 1994; Brink et al., 2000). Coupling of the  $\alpha_2$ -subtypes to cAMP inhibition has also been reported to display some agonist-specific differences (Kukkonen et al., 1998). Moreover, it has been demonstrated that receptor subtypes differ with respect to their coupling efficiencies to adenylate cyclase (Jansson et al., 1994a, 1994b). Recent studies have demonstrated that the modulation of cAMP production occurs in both subtype- and agonist-specific manner for  $\alpha_{2A/D}$ -receptors and in a subtype-specific manner for  $\alpha_{2B}$ - and  $\alpha_{2C}$ -receptors (Rudling et al., 2000). Trafficking of receptor signaling has also been shown to be agonist-dependent (Brink et al., 2000).

Activation of  $\alpha_2$ -receptors may lead to the suppression of  $Ca^{2+}$  entry into the nerve terminal, thereby causing an inhibition of neurotransmitter release (Berkowitz and Schwinn, 1994; Gertler et al., 2001). All  $\alpha_2$ -subtypes couple to  $Ca^{2+}$  elevation and do so in a similar manner (Kukkonen et al., 1998). With regard to  $Ca^{2+}$  elevation, different agonists may display characteristic subtype-specific differences in potency and activity (Kukkonen et al., 1998). Acceleration of  $Na^+/H^+$  exchange and activation of phospholipase  $A_2$  and C are some examples of other G-protein-linked second messenger mechanisms associated with  $\alpha_2$ -adrenoceptor activation (Limbird, 1988; Cotecchia et al., 1990; Ruffolo and Hieble, 1994; Aantaa et al., 1995; Kukkonen et al., 1998).

### 5.3.3. Location of alpha-2-adrenoceptors

Alpha-2-adrenoceptors are found in both central and peripheral nervous systems and located on both pre- and postsynaptic neurons. They are also found in some non-neuronal tissues (Bylund and U'Prichard, 1983; van Zwieten and Timmermans, 1984; Exton, 1985; Wang et al., 1996; Kable et al., 2000; Shi et al., 1999; 2000).

With the help of *in situ* hybridization, immunohistochemistry and other techniques,  $\alpha_2$ -subtypes have been demonstrated to follow distinct anatomical distribution patterns in the CNS of rats, mice and humans, although some species variation has been suggested (Tavares et al., 1996; Talley et al., 1996; Rosin et al., 1996; Wang et al., 1996; Lu and Ordway, 1997; Shi et al., 1999; Rosin, 2000; Shi et al., 2000). In the mouse brain,  $\alpha_{2A/D}$  is present in high densities in the sixth layer of the cortex and the locus caeruleus (LC);  $\alpha_{2B}$  is expressed predominantly in the thalamus and the Purkinje layer of the cerebellum; and  $\alpha_{2C}$  is expressed in the striatal (caudate-putamen) region (Wang et al., 1996) and in the LC (Lee et al., 1998; Osborne et al., 2002). Both  $\alpha_{2A/D}$  and  $\alpha_{2C}$  are found in high densities in the amygdaloid complex, hypothalamus, olfactory system and the hippocampal formation (Wang et al., 1996). The pattern of subtype distribution in the mouse brain correlates well with results obtained from *in situ* hybridization studies in rats (Mori et al., 1992; Nicholas et al., 1993; Scheinin et al., 1994; Tavares et al., 1996; Wang et al., 1996).

A heterogeneous distribution of  $\alpha_2$ -receptors is present in the spinal cord (Nicholas et al., 1993; Shi et al., 1999; 2000). In the rat spinal cord, for instance, high densities of  $\alpha_{2A/D}$  and  $\alpha_{2C}$  have been found in motoneurons and other cells in the ventral horns (Shi et al., 1999). In the dorsal horns, high densities of  $\alpha_{2A/D}$  exist in all layers as well as in the lateral spinal nucleus (Shi et al., 1999). Alpha-2B-receptors have been detected only in a few cells located superficially in the dorsal horn (Shi et al., 1999). This pattern of distribution suggests that  $\alpha_{2A/D}$  and  $\alpha_{2C}$  may play roles in the processing of both sensory and motor information, whereas  $\alpha_{2B}$  may be involved only in the processing of sensory information (Shi et al., 1999). The presence of all three subtypes in rat dorsal root ganglia

has been demonstrated, the most common being  $\alpha_{2C}$ , followed by  $\alpha_{2A/D}$ , with  $\alpha_{2B}$  found in only a few neurons (Shi et al., 2000).

Alpha-2-receptors have also been identified on blood platelets, melanocytes, peripheral noradrenergic and cholinergic axons, vascular and other smooth muscles, pancreatic  $\beta$ -cells, fat cells, in the gastrointestinal tract, liver, kidney, eye and spleen (Docherty et al., 1979; Drew and Whiting, 1979; Lasch and Jakobs, 1979; Samols and Weir, 1979; Timmermans et al., 1979; Aktories et al., 1980; Summers, 1984; Exton, 1985; Ruskoaho 1986; Pettinger, 1987; MacDonald et al., 1988a; Ruffolo and Hieble, 1994; Aantaa et al., 1995). *In vitro* studies have shown that the majority of arteries studied so far lack postsynaptic  $\alpha_2$ -receptors, whereas many veins in different species possess them (De Mey and Vanhoutte, 1981; Constantine et al., 1982; Shoji et al., 1983; Guimarães et al., 1987; Guimarães and Moura, 2001). In almost all veins,  $\alpha_{2A/D}$  has been the predominant subtype at the postsynaptic position, with the presence of some  $\alpha_{2C}$  suggested in human saphenous vein (Hicks et al., 1991; Blaylock and Wilson, 1995; Leech and Faber, 1996; Gavin et al., 1997; MacLennan et al., 1997). Presynaptic  $\alpha_2$ -receptors on the other hand, are common in both arteries and veins (Starke, 1987; Langer, 1997; Guimarães and Moura, 2001).

#### ***5.3.4. Functions of alpha-2-adrenoceptors***

In the nervous system, presynaptically located  $\alpha_2$ -receptors mediate inhibition of the release of noradrenaline, acetylcholine, serotonin, dopamine, substance P and possibly other neurotransmitters (Svensson et al., 1975; Göthert and Huth, 1980; Dubocovich, 1984; Ruskoaho, 1986; Curet et al., 1987; MacDonald et al., 1988a; Ruffolo and Hieble, 1994; Aantaa et al., 1995). In the brain and spinal cord, pre- and postsynaptically located receptors mediate inhibition of neuronal firing, suppression of neuronal excitability, sedation, sleep, antinociception, hypotension, bradycardia and other responses (Kobinger, 1978; van Zwieten and Timmermans, 1984; Ruskoaho, 1986; Curet et al., 1987; MacDonald et al., 1988a; Ruffolo and Hieble, 1994; Aantaa et al., 1995). In addition,  $\alpha_2$ -receptors mediate smooth muscle contraction, platelet aggregation and granule release,

contraction of capsule in the spleen, decrease in salivation, intestinal secretion and bowel motility, glycogenolysis, inhibition of lipolysis, inhibition of ADH release, blocking of ADH's effect in the renal tubules, increase in glomerular filtration rate, inhibition of renin release, increase in secretion of Na<sup>+</sup> and H<sub>2</sub>O, decrease in intra-ocular pressure, decrease in insulin release, stimulation of growth hormone release from the anterior pituitary and other responses (Lasch and Jakobs, 1979; Samols and Weir, 1979; Aktories et al., 1980; Ruskoaho, 1986; Pettinger et al., 1987; MacDonald et al., 1988a; Ruffolo and Hieble, 1994; Aantaa et al., 1995).

With the help of genetic engineering, knock-out studies and other experiments, knowledge about the functions of the  $\alpha_2$ -receptor subtypes has considerably improved in the past decade. Tables 1, 2 and 3 show the subtypes that mediate selected physiological responses.

**Table 1: Selected physiological responses mediated by the alpha-2A/D-adrenoceptor subtype**

<i>Response</i>	<i>Reference</i>
Leading role in regulating presynaptic inhibition of neurotransmitter release	Hein et al., 1999; Kable et al., 2000
Sedation	Hunter et al., 1997; Lakhani et al., 1997; Sallinen et al., 1997
Antinociception / analgesia	Hunter et al., 1997; Lakhani et al., 1997
Major role in mediating hypothermia	Hunter et al., 1997
Anaesthetic-sparing effect of alpha-2-adrenoceptor agonists	Lakhani et al., 1997
Antiepileptogenic effect of alpha-2-adrenoceptor agonists	Janumpalli et al., 1998
Possibly vasoconstriction in some vasculature	MacMillan et al., 1996
Centrally mediated hypotension and bradycardia	MacMillan et al., 1996; Nicholas et al., 1996; Altman et al., 1999; Zhu et al. 1999
Vascular relaxation (via increased endothelial production of N <sub>2</sub> O)	Bockman et al. 1993
Lipid metabolism	Tarkovacs et al., 1994
Possibly regulates dopaminergic and serotonergic systems	Sallinen et al., 1997

**Table 2: Selected physiological responses mediated by the alpha-2B-adrenoceptor subtype**

<i>Response</i>	<i>Reference</i>
Plays a role in mediating antinociceptive effect of N <sub>2</sub> O and may modulate other nociceptive responses in the spinal cord	Graham et al., 1997; Sawamura et al., 2000.
Vasoconstrictor (hypertensive) response to alpha-2-adrenoceptor agonist	Link et al., 1996; Kable et al., 2000
Salt-induced hypertension	Makaritsis et al., 1999
May play a role in developmental or reproductive processes	Link et al., 1996; Makaritsis et al., 1999; Hein et al., 1999

**Table 3: Selected physiological responses mediated by the alpha-2C-adrenoceptor subtype**

<i>Response</i>	<i>Reference</i>
Regulates presynaptic inhibition of neurotransmitter release	Hein et al., 1999
May play a minor role in mediating hypothermia	Sallinen et al., 1997
Possible role in regulating dopaminergic systems in the brain	Sallinen et al., 1997; Kable et al., 2000
Possible role in mediating stress-dependent depression	Sallinen et al., 1999
May play a role in modulating motor behaviour	Björklund et al., 1998
May modulate execution of complex navigation patterns	Björklund et al., 1999; 2000; Kable et al., 2000
Suspected to play a role in modulating memory process	Björklund et al., 1998
Suspected to play a role in mediating behaviour	Sallinen et al., 1998

#### **5.4. Mechanisms by which alpha-2-adrenoceptor agonists induce sedation, antinociception/analgesia and cardiovascular effects**

##### **5.4.1. Sedation and antinociception/analgesia**

The  $\alpha_2$ -agonists induce sedation by activating autoreceptors of the  $\alpha_{2A/D}$  subtype in the LC – the predominant noradrenergic nucleus in the brain and an important modulator of vigilance – thereby reducing its spontaneous rate of firing (Nacif-Coelho et al., 1994; Hunter et al., 1997; Lakhani et al., 1997; Kable et al., 2000). A decrease in the turnover of noradrenaline in the CNS also contributes to sedation (MacDonald et al., 1988b).

The precise mechanisms by which  $\alpha_2$ -agonists induce antinociception/analgesia have not been fully clarified (Gertler et al., 2001). These drugs may stimulate receptors at various sites in the pain pathway. Supraspinal and spinal mechanisms have been implicated in the modulation of nociceptive signal transmission in the CNS, leading to antinociception/analgesia, following the administration of  $\alpha_2$ -agonists (Pertovaara et al., 1991; 1993; Gertler et al., 2001). The  $\alpha_{2A/D}$  is the predominant subtype involved (Hunter et al., 1997; Lakhani et al., 1997). Spinal  $\alpha_{2B}$  may also contribute to modulating nociceptive responses in some pain modalities following the administration of  $\alpha_2$ -agonists (Graham et al., 1997). Alpha-2C possibly contributes to  $\alpha_2$ -agonist-induced spinal antinociception and synergy with opioids (Fairbanks et al., 2002). It has also been suggested that peripheral  $\alpha_2$ -receptors may mediate antinociception (Nakamura et al., 1988). Activation of G-protein-gated inwardly rectifying  $K^+$  (GIRK) channels resulting in membrane hyperpolarization with a subsequent decrease in the firing rate of excitable cells in the CNS (the nerve is prevented from firing) and the reduction of  $Ca^{2+}$  conductance into cells with subsequent inhibition of neurotransmitter release (the nerve cannot propagate its signal to its neighbour) are two different mechanisms which cause antinociception/analgesia (Gertler et al., 2001). A strong association exists between opioids and  $\alpha_2$ -receptors in the spinal cord (Unnerstall, 1984) such that synergism occurs following simultaneous administration of opioids and  $\alpha_2$ -agonists (Ossipov et al., 1990; Omote et al., 1991).

#### ***5.4.2. Cardiovascular effects***

Administration of an  $\alpha_2$ -agonist may induce a biphasic blood pressure response in humans and animals (especially following I.V. dosing), that is characterized by an initial transient hypertensive phase which is accompanied by a hypertension-induced-baroreceptor-reflex decrease in heart rate and followed by a hypotensive phase and stabilization of heart rate to below baseline values (Savola, 1989; Vainio and Palmu, 1989; Bloor et al., 1992; Dyck et al., 1993; Xu et al., 1998; Hall et al., 2000; Gertler et al., 2001). Alpha-2-agonists stimulate central and peripheral  $\alpha_2$ -receptors to induce these changes. When receptors in the brain, including the nucleus tractus solitarius – a major

centre for autonomic control – are stimulated, vagal tone is increased and sympathetic activity decreased, leading to bradycardia and hypotension (Hayashi and Maze, 1993; Cullen, 1996). Inhibition of noradrenaline production following presynaptic  $\alpha_2$ -receptor activation also reduces sympathetic tone and contributes to bradycardia (Cullen, 1996). The activation of postsynaptic  $\alpha_2$ -receptors in blood vessels may lead to hypertension (Ruffolo, 1985; Savola, 1989; Venugopalan et al., 1994) and this is mediated in part by the peripheral  $\alpha_{2B}$ , whereas the central  $\alpha_{2A/D}$  mediates hypotension and bradycardia (Kable et al., 2000). Medetomidine, an  $\alpha_2$ -agonist, has no direct action on cardiac muscles (Day and Muir, 1993).

### **5.5. Inverse, protean and ligand-specific agonism**

A full agonist induces full receptor activation, leading to the production of maximal receptor-mediated response; a partial agonist induces submaximal receptor activation, leading to submaximal receptor-mediated response and possible blockade of full agonist activation; and a neutral antagonist produces no physiological response, instead blocking responses to endogenous and exogenous agonists (Kenakin, 2001).

Until recently, the major targets of drug development have been full and partial agonists and antagonists (Kenakin, 2001). Ligands can, however, block system constitutive response (inverse agonists), behave as positive and inverse agonists on the same receptor (protean agonists) or differ in the stimulus pattern they produce in different physiological systems (ligand-selective agonist) (Kenakin, 2001). A receptor exists in an equilibrium between inactive R and active R\* conformational states (Milligan et al., 1995; Weiss et al., 1996). Binding of an agonist stabilizes R\* and induces a cellular response (Milligan et al., 1995; Wade et al., 2001). High receptor levels can increase the concentration of R\* and induce a response in the absence of an agonist (Milligan et al., 1995; Wade et al., 2001). Inverse agonists preferentially bind to R and inhibit basal receptor activity, whereas neutral antagonists bind equally well to R and R\*, with no effect on receptor activity, while retaining the ability to block the effects of both agonists and inverse agonists (Wade et al., 2001). Recent studies have indicated that not all antagonists display

a total lack of intrinsic efficacy but that some, at least in certain situations, may display inverse agonism (Milligan et al., 1995; Wade et al., 2001), a concept that has received considerable attention of late. Many alpha-2-adrenoceptor agents popularly known to be antagonists at alpha-2-adrenoceptors – e.g. yohimbine, rauwolscine and RX821002 - have recently been found to display inverse agonism in some systems (Cayla et al., 1999; Murrin et al., 2000; Wade et al., 2001).

#### **5.6. Use of alpha-2-adrenoceptor agonists in veterinary medicine (information pertaining to cats follows separately in section 5.8.)**

Commonly used  $\alpha_2$ -agonists in veterinary practice include xylazine, detomidine, medetomidine (MED) and romifidine. Dexmedetomidine (DEX) is a drug currently undergoing development. Clonidine and brominidine have also been used occasionally for studies in animals. Clinical effects of these drugs are quite similar. The slight differences - manifested mainly in their durations of action, extent of adverse effects and a few other specificities - are attributed primarily to differences in their  $\alpha_2/\alpha_1$  selectivity ratios (Virtanen et al., 1988). The greater the degree of this selectivity, the less binding occurs at  $\alpha_1$ -receptor and other non-adrenoceptor sites and the less the undesirable neurological effects encountered (Ko et al., 1997). The rank order of this selectivity ratio for some of the above-mentioned drugs in rats, for instance, is as follows: MED > detomidine > clonidine > brominidine > xylazine (Virtanen et al., 1988). Detomidine and MED showed about 100 times stronger affinity for all  $\alpha_2$  subtypes than xylazine, but none of these three agonists displayed any subtype selectivity (Schwartz and Clarke, 1998). Different animal species may vary in their sensitivities to these drugs (Hall et al., 2001). The commonly used  $\alpha_2$ -agonists in horses and ruminants are xylazine and detomidine, and in dogs, cats, rabbits, rodents, ferrets and birds, xylazine and MED. MED has also been used in ruminants. DEX has been studied extensively in rodents (and humans), with limited studies reported in dogs, cats, sheep and other species. Romifidine is used mainly in horses and to some extent in ruminants and other animal species (Lemke, 1999a; Redondo et al., 1999; Aithal et al., 2001; Pypendop and Verstegen, 2001; Amarपाल et al., 2002).

In veterinary practice,  $\alpha_2$ -agonists are useful for providing sedation, analgesia and muscle relaxation (Greene, 1999). Small-sized, stressed and difficult animals may require larger doses to successfully induce these responses than bigger or calmer ones (Short, 1992; Ko et al., 1997; Greene, 1999). Analgesia induced by these drugs is usually of shorter duration than sedation (Short, 1992; Greene, 1999). Alpha-2-agonists have been used alone to perform various clinical examinations and manipulations. If analgesia induced by recommended doses of systemic  $\alpha_2$ -agonists is insufficient, it can be enhanced with the addition of opioids. Epidural administration of  $\alpha_2$ -agonists has been associated with longer duration of analgesia than systemic administration (Rector et al., 1998). These drugs have also been combined with other injectable or inhalational anaesthetics to improve their effectiveness. Combination of  $\alpha_2$ -agonists with dissociative agents, such as ketamine or tiletamine, is a common practice. The dissociative agents increase heart rate and induce poor muscular relaxation, whereas the  $\alpha_2$ -agonists reduce heart rate and induce good muscular relaxation. In combination, the shortcomings of both drugs are to some extent mutually compensated. Alpha-2-agonists reduce the dose requirements of other agents for the anaesthesia of animals.

### ***5.6.1. Xylazine***

Xylazine ([2-(2,6-dimethylphenylamino)-4H-5,5-dihydro-1,3-thiazine]; Rompun<sup>®</sup>) has been used alone and in combination with other agents to induce sedation, anaesthesia, analgesia and muscular relaxation in a variety of animal species. Xylazine used alone and in combination with such agents as ketamine, acepromazine, pentobarbital, halothane, morphine, butorphanol and guaifenesin have been described in dogs (Clark et al., 1982; Hatch et al., 1982; 1983; Cronin et al., 1983; Tranquilli et al., 1984), horses (Clarke and Hall, 1969; Tronicke and Vocke, 1970; Kerr et al., 1972; Hoffman 1974; Muir et al., 1977), ruminants (Clarke and Hall, 1969; Hopkins 1972; Campbell et al., 1979; Mbiuki 1982) swine (Breese and Dodman, 1984; Trim and Gilroy, 1985; Thurmon et al., 1986) and laboratory and non-domestic animals (Roughton 1975; Hughs, 1981; Hsu et al., 1981; Hsu and Shulaw, 1984). Among the domestic animals, cattle are most sensitive, whereas the pig is quite resistant to xylazine (Green and Thurmon, 1988).

### **5.6.2. Detomidine**

Detomidine ([4-(2,3-dimethylphenyl) methyl 1H imidazole]; Domosedan<sup>®</sup>) was first developed for use in cattle and horses as a sedative-analgesic (Virtanen et al., 1985). It is more potent than xylazine (Virtanen and MacDonald, 1985) and romifidine (Hamm et al., 1995). At equivalent doses, it induces sedation and analgesia of longer duration than xylazine in horses (Clarke and Taylor, 1986; Joche and Hamm, 1986; Lowe and Hifiger, 1986). Detomidine has been used alone and in combination with agents such as ketamine, tiletamine-zolazepam (Telazol) and butorphanol to induce sedation, anaesthesia and analgesia in horses (Clarke and Taylor, 1986; Clarke et al., 1986; LeBlanc, 1991; Lin et al., 1992; Hamm et al., 1995).

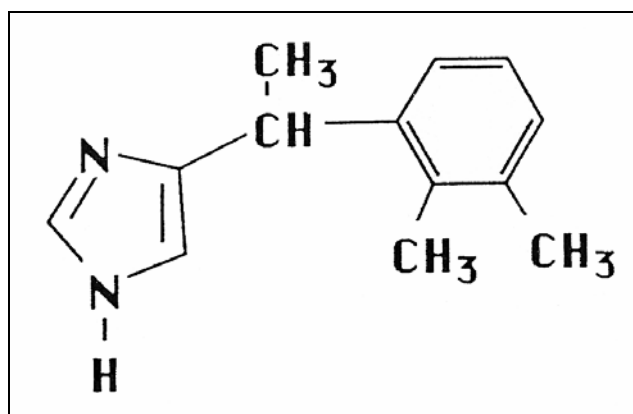
### **5.6.3. Romifidine**

Romifidine (2-[(2-bromo-6-fluorophenyl) imino] imidazole; Sedivet<sup>®</sup>) is an  $\alpha_2$ -adrenoceptor agonist developed from clonidine. It has been used alone to induce sedation in animals (England et al., 1992; Hamm et al., 1995; Lemke, 1999a; Freeman and England, 2000). It has also been used as a premedicant before general anaesthesia in horses (Freeman et al., 2000; Lucena et al., 2000; Rasis et al., 2000; Taylor et al., 2001), dogs (England et al., 1996; England and Hammond, 1997; Redondo et al., 1999; 2000; Martin et al., 2001) and goats (Saxena, 1997; Aithal et al., 2001). Butorphanol potentiated the sedative effect of romifidine (England and Watts, 1997). Romifidine induced analgesia with a ceiling effect following spinal administration in goats (Amarpal, 2002).

### **5.6.4. Medetomidine and dexmedetomidine**

Medetomidine ([ $\pm$  4-[1-(2, 3-dimethylphenyl) ethyl]-1 H-imidazole]; Domitor<sup>®</sup>) (Figure 1) is a highly potent, selective, specific and lipophilic  $\alpha_2$ -agonist (Savola et al., 1986). This drug is a racemic mixture of equal proportions of two optical enantiomers – the levo- and dextro-rotatory optical isomers (MacDonald et al., 1991; Savola and Virtanen,

1991) with generic names levomedetomidine (LEV) and dexmedetomidine (DEX) respectively. Pharmacological activity of MED is stereospecific and is due predominantly to its dextro-rotatory isomer (Segal et al., 1988; Virtanen et al., 1988; MacDonald et al., 1991; Savola and Virtanen, 1991; Kuusela et al., 2001a; 2001b; Kastner et al., 2001a; 2001b). At very high doses, however, the same LEV may display weak positive  $\alpha_2$ -agonistic properties in some systems (Savola and Virtanen, 1991; Jansson et al., 1994a; b; 1995; Kuusela et al., 2001b) and what has been described as  $\alpha_2$ -antagonistic (MacDonald et al., 1991) or inverse agonistic (Jansson et al., 1998) properties in other systems. LEV has therefore been termed a protean agonist (Jansson et al., 1998). In binding studies with rat brain preparations, the  $\alpha_2/\alpha_1$  selectivity ratio of MED was found to be 1620, which was 5-10 times higher than that for similar reference compounds like xylazine, brominidine, clonidine and detomidine (Virtanen et al., 1988). MED has very weak or no binding affinity for  $\beta_1$ ,  $\beta_2$ , adrenergic,  $H_1$ ,  $H_2$ , histamin, 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, muscarine, dopamine, tryptamine, GABA, opiate and benzodiazepine receptors (Virtanen et al., 1988).



**Figure 1.** Chemical structure of medetomidine

#### ***5.6.4.1. Some pharmacokinetic data on MED and DEX***

Following S.C. (rat) and I.M. (dog) administration, MED is rapidly absorbed into the blood stream and rapidly distributed into well-perfused tissues, including the brain,

effectively penetrating these tissues and readily reaching its target receptors (Salonen 1989). Rapid absorption of DEX into the CSF (following epidural administration) or the blood stream (following transdermal patch application) has also been reported (Eisenach, 1994; Kivistö et al., 1994). A relatively low proportion (approximately 15%) of MED exists as a free unbound fraction in circulation, while most of it circulates in its inactive protein-bound form. Elimination occurs mainly by biotransformation in the liver, the rate of which may be controlled by hepatic blood flow (Salonen, 1989). MED is rapidly excreted mostly via the urine as metabolites with no pharmacological activity, and only traces of the drug are excreted unchanged (Salonen, 1989). The therapeutic effects of MED are terminated by removal from its target tissue, which parallels the elimination of the drug from blood plasma (Salonen, 1989). The pharmacokinetics of DEX and MED in dogs (I.V. administration) are similar, but the clearance of LEV is more rapid (Kuusela et al., 2001a). Both DEX and LEV inhibit human cytochrome P-450 catalytic activity equally (Kharasch et al., 1992). It has also been demonstrated that both isomers inhibit microsomal drug metabolism in rat and human livers (Pelkonen et al., 1991). At equally effective concentrations, DEX may possess a lower potential for drug interactions than MED (Kharasch, et al., 1992).

#### ***5.6.4.2. Sedative and antinociceptive/analgesic effects of MED and DEX***

Sedation and analgesia induced by MED in animals are dose-dependent and reach ceiling points beyond which increasing the dose may only prolong the duration of these responses but not their intensities (Vainio et al., 1989).

MED and DEX have been administered I.V. or I.M. to effectively sedate dogs (Bergstrom, 1988; Clarke and England, 1989; Vainio et al., 1989; Vainio and Palmu, 1989; Vähä-Vahe, 1989; Vainio, 1990; Vainio and Vähä-Vahe, 1990; Young et al., 1990; Cullen and Reynoldson, 1993; Ko et al., 1997). Intravenous administration results in a more rapid onset and more profound sedation with a relatively shorter duration (Ko et al., 1997). The oral route has been reported to be ineffective due to an extensive hepatic first-pass effect, with some pharmacological effect achievable only at very high doses of the

drug (Vainio, 1989). Sublingual administration yielded effective sedation in dogs, although less profound than an identical dose given I.M. (Hall et al., 1994).

Opioids, such as butorphanol, fentanyl, morphine, oxymorphone, pethidine and buprenorphine, have been combined with MED systemically to enhance sedation-analgesia in dogs (England and Clarke, 1989; Bartram et al., 1993; Ko et al., 1997; Greene, 1999; Guller et al., 2001; Robinson et al., 2001). MED has also been administered alone or in combination with opioids epidurally to induce analgesia in dogs (Branson et al., 1993; Vesal et al., 1996). Intrathecal DEX was effective for inducing antinociception in sheep (Eisenach et al., 1994).

#### ***5.6.4.3. Cardiovascular and pulmonary effects of MED and DEX***

MED decreased mean arterial pressure, cardiac output and myocardial oxygen requirements in halothane-anaesthetised dogs (Vickery et al., 1988). DEX increased coronary vascular resistance and myocardial oxygen extraction and reduced coronary (Flacke et al., 1993) and cerebral blood flows without affecting the cerebral metabolic rate for oxygen in dogs (Karlsson et al., 1990; Zornow et al., 1990). Equivalent doses of MED and DEX (administered at half the dose of MED) induced similar cardiovascular changes in sheep (Kastner et al., 2001a; 2000b).

The anticholinergics atropine and glycopyrrolate are capable of reversing alpha-2-agonist-induced bradycardia in dogs but may cause tachycardia and hypertension (Alibhai et al., 1996), making their use quite controversial (Alibhai et al., 1996; Greene, 1999). However, when required, (e.g. during ocular surgery), they should be administered preemptively (about 10 min before MED) (Short, 1991; 1992). It has been recommended that possible MED-induced severe sinus bradycardia or atrioventricular block be corrected by administering the alpha-2-antagonist atipamezole (Short, 1992; Greene, 1999).

MED decreased the rate of respiration to different degrees and for variable durations in dogs (Vainio and Palmu, 1989; Vainio, 1990; Hammond and England, 1994; Venugopalan et al., 1994). MED slightly increased arterial carbon dioxide tension in dogs (Vainio, 1989; Cullen and Reynoldson, 1993). Some dogs sedated with MED and breathing room air turned cyanotic (Clarke and England, 1989; England and Clarke, 1989a; Vähä-Vahe, 1989; Sap and Hellebrekers, 1993), possibly due to venous desaturation (England and Clarke, 1989a; Vähä-Vahe, 1989; Sap and Hellebrekers, 1993; Cullen, 1996).

#### ***5.6.4.4. Anaesthetic-sparing effect of MED and DEX and the combination of MED or DEX with other injectable drugs***

Premedication with MED or DEX decreased anaesthetic requirements during anaesthesia with thiopental sodium, halothane and nitrous oxide (Bergstrom, 1988; Young et al., 1990), propofol and halothane (Bufalari et al., 1997), propofol and isoflurane (Kuusela et al., 2001a) propofol (Vainio, 1991; Cullen and Reynoldson, 1993; Hammond and England, 1994; Bufalari et al., 1996), isoflurane (Ewing et al., 1993) and halothane (Vickery et al., 1988; Segal et al., 1989) in dogs. A recent study suggests that, as a premedicant to general anaesthesia, MED may possess comparatively better potential to attenuate perioperative stress responses in dogs than sedatives such as acepromazine (Vaisanen et al., 2002). MED or DEX has also been used as a premedicant before general anaesthesia in rabbits, sheep and horses (Flecknell and Liles, 1996; Kastner et al., 2001a; b; Yamashita et al., 2002). In horses premedicated with MED, transition to inhalational anaesthesia was smoother than those premedicated with xylazine (Yamashita et al., 2002).

Combining ketamine with MED or DEX has been very common. MED has been used with ketamine to induce anaesthesia for diagnostic and minor to moderately painful surgical procedures in different animal species (Mero et al., 1989; Nevalainen et al., 1989; Mohammed et al., 1991; Raekallio et al., 1991; 1994; 1998; Tulamo et al., 1995; Hellebrekers et al., 1997; Hoffman et al., 2002). MED has also been combined with

ketamine for the immobilization and anaesthesia of small and large non-domestic felids (Jalanka, 1988; 1989; Lewis, 1994; Langan et al., 2000).

**5.7. Use of alpha-2-adrenoceptor antagonists in veterinary medicine (information pertaining to cats follows separately in section 5.8.)**

Yohimbine (17-hydroxy-yohimban-16-carboxylic acid methyl ester) has been used to antagonize  $\alpha_2$ -agonist-induced effects in different animal species (Hall et al., 2001; Gross and Booth, 1995). It may, however, cause excitation if administered in excess (Hall et al., 2001; Lemke, 1999b). Tolazoline (2-benzyl-2-imidazoline) has been administered to a number of species to reverse the depressant effects of xylazine (Gross and Booth, 1995; Lemke, 1999b). Tolazoline induces  $H_2$ -receptor agonist action and has been associated with gastrointestinal complications (Gross and Booth, 1995; Lemke, 1999b).

Atipamezole ([4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole]; Antisedan<sup>®</sup>) is a highly potent, selective and competitive  $\alpha_2$ -antagonist with an  $\alpha_2/\alpha_1$  selectivity ratio 200-300 times greater than that of yohimbine or idazoxan and is devoid of activity at other types of receptors (Virtanen et al., 1989). It has been used to reverse xylazine-, detomidine- and MED-induced sedation, analgesia and other effects in various animal species (Jalanka, 1988; 1989; Savola, 1989; Vainio and Vähä-Vahe, 1990; Vähä-Vahe, 1990a; 1990b; Hall et al., 2001; Cullen, 1996; Langan et al., 2000). Of much clinical importance to veterinary practice, however, is its ability to shorten the duration of sedation, mobilize the patient after non-invasive or minor surgical intervention and reverse  $\alpha_2$ -agonist-induced cardiovascular side-effects (Ko et al., 1997). In dogs, an I.M. dose of 4-6 times the preceding dose of MED has been found to be effective (Clarke and England, 1989; Vähä-Vahe, 1990a; Vainio, 1990; Vainio and Vähä-Vahe, 1990), with arousal occurring about 3-5 min after injection (Cullen, 1996). Side-effects are minor and may include micturation, salivation, vomiting, muscle tremors, relapse into drowsiness, over-alertness (Vähä-Vahe, 1990a), panting, soft or liquid faeces, vasodilation of sclera (Ko et al., 1997) and a brief reduction of arterial blood pressure shortly before reversal of MED-induced hypotension (Vainio, 1990). Since the drug simultaneously reverses

$\alpha_2$ -agonist-induced analgesia, it has been recommended that patients likely to have postprocedural pain should be reversed only if other pain relief medication has been given (Ko et al., 1997). Dosage recommendations vary with species and the  $\alpha_2$ -agonist used (Gross and Booth, 1995; Lemke, 1999b).

## **5.8. Alpha-2-adrenoceptor agonists and antagonists in cats**

The most commonly used  $\alpha_2$ -agonists in cats are xylazine and MED. Isolated reports are also available on the use of detomidine or romifidine. Clonidine has occasionally been used for experimental purposes.

### **5.8.1. Xylazine, detomidine and romifidine**

Xylazine at 1-3 mg/kg I.M. has been used to induce effective sedation in cats (Greene and Thurmon, 1988; Hall et al., 2001). Higher doses may produce significant respiratory depression (Amend, 1973; Greene and Thurmon, 1988). The drug induces vomiting in most cats within 3-8 min of its administration (Moye et al., 1973; Gross and Booth, 1995). A dose of 0.66 mg/kg (I.M.) was found to be reliable (Colby et al., 1981) with 1.1 mg/kg considered to be optimal for inducing vomiting (Amend et al., 1972; Gross and Booth, 1995). Several different xylazine-ketamine dose combinations have been used to induce anaesthesia in cats lasting 15-60 min depending on the doses of drugs used. Xylazine substantially decreased the dose of barbiturate required for anaesthesia in cats (Hatch et al., 1984; Gross and Booth, 1995).

Detomidine (500  $\mu$ g/kg) has been administered alone or in combination with ketamine (5-10 mg/kg) orally to induce effective sedation in cats (Wetzel and Ramsay, 1998; Grove and Ramsay, 2000). Romifidine (80-120  $\mu$ g/kg) induced effective sedation, and when combined with ketamine (7.5 mg/kg), induced 30-40 min of anaesthesia with good muscle relaxation and analgesia in cats (Verstegen et al., 1995). Anaesthesia induced with the MED (80  $\mu$ g/kg)-ketamine (7.5 mg/kg) combination was, however, comparatively longer lasting (more than 90 min), with a better degree of analgesia and

muscular relaxation (Verstegen et al., 1995). Apnoea occurred in one cat that received levomepromazine, romifidine and ketamine, therefore, ventilatory support may be necessary when this combination is used (Cruz et al., 2000).

### **5.8.2. Medetomidine and dexmedetomidine**

MED has been approved for use in cats (Debuf, 1991; Ko et al., 1997). It has been safely administered via I.M. (Stenberg et al., 1987; Vähä-Vahe, 1989), epidural (Duke et al., 1994) and I.P. (Pertovaara et al., 1991a) routes to induce sedation and/or analgesia. MED has been applied topically to the eye in cats to reduce intra-ocular pressure (Jin et al., 1991). DEX (Farber et al., 1999) and MED (Grove and Ramsay, 2000) have been administered orally in cats. The I.M. route is the most popular.

#### **5.8.2.1. Pharmacokinetics of MED and DEX**

Following an I.M. administration of 80 µg/kg MED in cats, absorption occurred rapidly. Peak serum concentration (24.6 ng/ml) was reached within 15 min of drug administration and absorption half-life was 8 min (Salonen, 1989). Distribution occurred rapidly and tissue penetration was effective (Salonen, 1989). The apparent volume of distribution was found to be 3.5 l/kg and most of the drug existed in circulation in its inactive protein-bound form, with only 15% remaining as a free fraction (Salonen, 1989). Half-life of elimination was 1.35 hrs and total clearance was 29.5 ml/min kg (Salonen, 1989). About two-thirds of the original dose of drug was excreted via urine, mostly as pharmacologically inactive metabolites during the first 24 hrs after dosing, with very little found in faeces (Salonen, 1989). Unlike in other animals, cat urine contained no or negligible amounts of β-glucuronidase hydrolysable conjugates (Salonen, 1989).

#### **5.8.2.2. Sedative and antinociceptive/analgesic effects of MED and DEX**

MED at doses ranging from 50 to 200 µg/kg has been used successfully to induce dose-dependent sedation and analgesia in cats following systemic administration (Vainio et al.,

1986/1987; Vähä-Vahe, 1989). Different authors have suggested various optimal doses for clinical use within the range of 50 - 150 µg/kg (Vainio, 1989; Vähä-Vahe, 1989; Short, 1992; Cullen, 1996). Within this dose range, excited and/or small animals, kittens under 6 months old and in some instances, pregnant queens may need a higher dose, due probably to increased metabolic rate or increased sympathetic tone (Short, 1992). The drug at 20-180 µg/kg (I.M.) induced dose-dependent drowsiness or sleep-like state in cats (Stenberg et al., 1987). Clinically useful sedation lasted 45, 90 and 98 min following I.M. administration of 50, 100 and 200 µg/kg, respectively (Vainio, 1986/1987), and drowsiness persisted for more than 4 hrs after 180 µg/kg I.M. (Stenberg et al., 1987). For effects on vigilance, MED – 180 µg/kg was found to be comparable with xylazine – 3 mg/kg (Stenberg et al., 1987). A low epidural dose of MED (10 µg/kg) induced about 15-25 min of profound and 30-90 min of mild sedation in cats (Duke et al., 1994). A high dose of DEX reduced seizure threshold during enflurane (3.5%) anaesthesia in cats (Miyazaki et al., 1999).

MED induces dose-dependent analgesia in cats (Vainio, 1989; Pertovaara et al., 1991a), which is of relatively short duration (shorter than sedative effect), following systemic administration (Vainio et al., 1986/1987; Short, 1992). In pentobarbitone-anaesthetised cats, MED (30-100 µg/kg I.P.) dose-dependently raised the threshold of the tooth pulp-evoked jaw-opening reflex – a trigeminal reflex considered to be predominantly nociceptive (Pertovaara et al., 1991a). Epidural administration of MED (10 µg/kg) effectively induced analgesia in cats, lasting about 4 hrs in the hind limbs and about 2 hrs in the forelimbs (Duke et al., 1994).

### ***5.8.2.3. Cardiopulmonary and other side-effects of MED and DEX***

MED or DEX induces bradycardia in cats (Stenberg et al., 1987; Savola, 1989; Daniel et al., 1997; Selmi et al., 2003). The drug induces initial transient hypertension followed by hypotension in anaesthetised cats (Savola, 1989; Duke et al., 1994). Within 5 min after administration of MED (80 µg/kg I.M.) and ketamine (5 mg/kg I.M.) in cats, heart and respiratory rates decreased by 31% and 70%, respectively, and systolic blood pressure

had been increased by 69% (Dobromylskyj, 1996). In healthy isoflurane-anaesthetised cats, MED – 20 µg/kg (I.M.) has been reported to cause decreases in heart rate, cardiac index, stroke index, rate pressure product, right and left ventricular stroke work index, and increases in; systemic vascular resistance and central venous pressure, while systolic, mean and diastolic arterial pressures, pH, pO<sub>2</sub> and pCO<sub>2</sub> remained identical to baseline values (Lamont et al., 2001). In another study, epidural MED – 10 µg/kg increased arterial pCO<sub>2</sub> and decreased pH in isoflurane-anaesthetised cats (Duke et al., 1994). A low dose of MED (10 µg/kg I.M.) has also been reported to cause vasoconstriction in isoflurane-anaesthetised cats, leading to sustained increases in left ventricular preload and afterload (Golden et al., 1998). Based on this observation, Golden and colleagues (1998) suggested that MED in combination with isoflurane should be avoided or used cautiously in cats in which sudden increase in ventricular preload or afterload could be detrimental. Administration of MED (10 µg/kg I.M.) similarly caused a decrease in left ventricular function (left ventricular ejection fraction, peak ventricular ejection rate and peak ventricular filling rate decreased) in isoflurane-anaesthetised cats leading to the conclusion that MED-induced impairment of systolic and diastolic cardiac function is deleterious in cats with underlying heart disease (Daniel et al., 1997). A recent study suggested that MED may be a suitable sedative-analgesic for cats with left ventricular outflow tract (LVOT) obstruction since the drug decreases heart rate, LVOT velocity and LVOT pressure gradient (Lamont et al., 2002). DEX (15 µg/kg P.O.) used alone did not alter pressor responses in cats, but when combined with halothane, attenuated these responses in a synergistic manner (Farber et al., 1999). DEX-induced bradycardia was also greater in the presence of halothane. Taken together these findings led the authors to conclude that DEX has an anaesthetic-sparing effect on some CNS-mediated cardiovascular control mechanisms and that DEX does not attenuate brain-mediated increases in blood pressure on its own, but in combination with halothane, acts to modulate central cardiovascular responses in cats (Farber et al., 1999).

About 65-90% of cats vomit either during the induction of sedation or during the recovery period (Vainio, 1989; Vähä-Vahe, 1989; Duke et al., 1994). Since vomiting is due to stimulation of the central emetic-trigger zone in the brain, fasting the cat before

induction will not necessarily prevent its occurrence (Vainio, 1989). Hypothermia may accompany the administration of MED in cats (Vainio, 1989).

#### **5.8.2.4. Combination of MED or DEX with other drugs**

MED has been combined with various drugs to achieve anaesthesia and analgesia in cats. Most common among these is ketamine. In combination with MED, the two drugs mutually compensate for some of their individual shortcomings. In a MED-ketamine combination in cats, adequate muscular relaxation was achieved and analgesia improved (Verstegen et al., 1989; 1990; 1991a; Becker and Oechtering, 1997). Verstegen and others (1989; 1990; 1991a) studied MED (80 µg/kg) combined with various doses of ketamine undergoing ovariohysterectomy, compared these combinations with acepromazine-ketamine, xylazine-ketamine and zolazepam-tiletamine combinations and found that the MED (80 µg/kg)-ketamine (5-7.5 mg/kg) combination induces adequate anaesthesia for ovariohysterectomy, good muscular relaxation, good analgesia, has minimal side-effects, requires a low dose of ketamine and in comparison with the xylazine-ketamine combination, induces a longer duration of anaesthesia and better analgesia.

The MED-ketamine combination induced similar side-effects as the xylazine-ketamine combination, including vomiting, salivation, apnoea, muscle jerking and tremor (Verstegen et al., 1990). Salivation occurred in up to 10% of cats during induction of anaesthesia with MED (50 µg/kg I.M.)-ketamine (10 mg/kg I.M.), and this was attenuated with atropine (Becker and Oechtering, 1997). Incidence of pain on I.M. injection of MED-ketamine combination in cats (Verstegen et al., 1990; Young and Jones, 1990; Becker and Oechtering, 1997) has been reduced by performing the injection slowly.

Becker and Oechtering (1997) anaesthetised cats with the MED (50 µg/kg I.M.)-ketamine (10 mg/kg I.M.) combination and managed to perform various short-lasting (average duration 30 min) procedures. For longer procedures (average duration 85 min) and

procedures caudal to the diaphragm, the cats also received epidural anaesthesia, and for even longer-lasting procedures (average duration 100 min) and procedures cranial to the diaphragm, anaesthesia was maintained with inhalational agents (Becker and Oechtering, 1997). Cats that were anaesthetised with MED-ketamine for ovariohysterectomy had significantly less postoperative pain than those anaesthetised with a combination of acepromazine-thiopentone-halothane (Slingsby et al., 1998).

MED or DEX has been combined with tiletamine-zolazepam to induce anaesthesia and with opioids, such as butorphanol, oxymorphone or morphine, to enhance sedation-analgesia in cats (Greene, 1999; Selmi et al., 2003). These drugs have also been combined with local anaesthetics (e.g. lidocaine) to perform minor surgeries. Premedication with MED has been found to decrease the doses of propofol (Bufalari et al., 2000), volatile and other anaesthetics (Becker and Oechtering, 1997) required for anaesthesia.

#### *5.8.2.5. Alpha-2-adrenoceptor antagonists in cats*

Yohimbine, idazoxan and atipamezole have been used effectively to antagonize the effects of  $\alpha_2$ -agonists in cats (Hsu and Lu, 1984; Savola, 1989; Short 1992; Brearley, 1994), with atipamezole being the most popular.

##### *5.8.2.5.1. Atipamezole in cats*

Atipamezole antagonizes the effects of MED when MED is used alone (Vähä-Vahe, 1990b) or in combination with other drugs (Young and Jones, 1990; Verstegen et al., 1991b). Atipamezole at doses 2-4 times the preceding dose of MED was effective for reversing MED-induced sedation (Stenberg et al., 1993) and bradycardia (Vähä-Vahe, 1990b) in cats. The drug reverses sedation within 5 min of I.V. and within 10 min of I.M. administration. Atipamezole effectively antagonized the hypotensive and bradycardic effects of MED in anaesthetised cats (Savola, 1989). Atipamezole-induced reversal of MED in a MED-ketamine combination was associated with smooth recovery with no side-effects (Young and Jones, 1990; Becker and Oechtering, 1997) other than ataxia and

muscular inco-ordination attributed to unantagonized ketamine (Verstegen, 1991b). Cats may be exposed to the side-effects of ketamine if MED is completely antagonized too early after administering the combination (Verstegen, 1991b).

## **6. AIMS OF THE STUDY**

The aims of this study were:

- 1) to evaluate the effectiveness of oral-mucosal application of medetomidine for sedation in cats (I).
- 2) to evaluate and compare the sedative and analgesic effects of parenterally administered medetomidine and dexmedetomidine in cats (II, III).
- 3) to study the use of medetomidine for postoperative analgesia in cats (IV).
- 4) to determine the relationship between plasma and CSF concentrations of medetomidine and how these concentrations vary with the level of sedation in experimental rabbits (V).

## 7. MATERIALS AND METHODS

The following is a brief summary of the materials and methods used in the studies. Further details can be found in the respective original studies.

### 7.1. Animals and study design

Information on the animals used in the study designs is presented in Table 4. The cats in Studies I, II and III were neutered and purpose-bred. They were allowed a period of at least 4 weeks prior to the beginning of the studies, to become acclimatized to the environment at the clinic where the experiments were performed. Cats in Study IV were client-owned pets presented to the University of Helsinki's Small Animal Teaching Hospital for routine elective ovariohysterectomy. Informed owner consent was obtained before these cats were included in the study. Laboratory rabbits were used in Study V. All animals in the studies were clinically healthy. All cats were fasted for at least 12 hrs before anaesthesia. Water was available *ad libitum* whenever the cat was awake. Food and water were always available to the rabbit.

**Table 4: Animals and study designs used in original studies I-V**

	<i>Study I</i>	<i>Study II</i>	<i>Study III</i>	<i>Study IV</i>	<i>Study V</i>
<i>Animals</i>	Cats	cats	cats	cats	rabbits
<i>Number used</i>	7	6*	6	64	23
<i>Gender</i>	4 m 3 f	4 m 2 f	4 m 2 f	f	f
<i>Age (yrs)</i>	0.6 – 8	1 – 9	1 – 9	≥ 0.5	0.3 - 2
<i>Weight (M ±SD) kg</i>	3.60 ± 0.65	4.42 ± 0.66	4.38 ± 0.79	3.32 ± 0.69	3.80 ± 1.30
<i>Study design</i>	randomised, cross-over, experimental	randomised, blinded, cross-over, experimental	randomised, blinded, cross-over, experimental	randomised, blinded, clinical, placebo-controlled, experimental	pretest-posttest, experimental

m = male; f = female; M = mean; SD = standard deviation \* = these cats were also used in Studies I and III

The inclusion of a placebo group (IV) was not unjustified since postoperative analgesic therapy was not a routine practice in all veterinary hospitals and clinics at the time of the

study (Flecknell, 1994; Dohoo and Dohoo, 1996; Capner et al., 1999; Raekallio et. al., 2003). In an attempt to assess the analgesic efficacy of carprofen in comparison with pethidine following ovariohysterectomy in cats, Lascelles and others (1995) similarly found it justified at that time, to include a placebo group.

## 7.2. Drugs used and routes of their administration

**Table 5: Doses of test drugs used in the various studies**

<i>Study</i>	<i>Test drug</i>	<i>Dose</i>	<i>Route</i>
<b>I</b>	MED	200 µg/kg	Oral § I.M.
<b>II</b>	MED	50 µg/kg 100 µg/kg 150 µg/kg	I.M. I.M. I.M.
	DEX	25 µg/kg 50 µg/kg 75 µg/kg	I.M. I.M. I.M.
<b>III*</b>	MED	0.50 µg/kg/min (step 1) 2.00 µg/kg/min (step 2) 8.00 µg/kg/min (step 3)	I.V. infusion (50 min) I.V. infusion (50 min) I.V. infusion (50 min)
	DEX	0.25 µg/kg/min (step 1) 1.00 µg/kg/min (step 2) 4.00 µg/kg/min (step 3)	I.V. infusion (50 min) I.V. infusion (50 min) I.V. infusion (50 min)
<b>IV</b>	MED butorphanol saline placebo	15.00 µg/kg 0.10 mg/kg	I.M. I.M. I.M.
<b>V</b>	MED	100 µg/kg	I.V. bolus

§ drug was sprayed into the mouth

\* infusion step 1 was preceded by a bolus I.M. dose of 20 µg/kg MED (or 10 µg/kg DEX), step 2 was preceded by 10 min of I.V. infusion at 4 µg/kg/min MED (or 2 µg/kg/min DEX) and step 3 by 10 min of I.V. infusion at 16 µg/kg/min MED (or 8 µg/kg/min DEX)

The drugs used in the studies were; MED (Domitor<sup>®</sup> Orion Corp., Turku, Finland) and DEX (Orion Corp, Turku, Finland), produced for research purposes and butorphanol (Torbugesic<sup>®</sup> Fort Dodge Laboratories, Fort Dodge, Iowa, USA) (Table 5). Ketamine (Ketalar<sup>®</sup> Parke-Davis & Co, Pontypool, Gwent, UK) was administered I.M. ( $7.0 \pm 1.3$  mg/kg) in combination with MED ( $118.5 \pm 24.3$  µg/kg) to anaesthetize the cats for ovariohysterectomy (IV) or administered alone I.V. (20 mg/kg) to anaesthetize the rabbits for CSF collection and heart puncture (V).

For oral administration, MED was sprayed into the mouth with a 1 ml syringe. Muscles of the caudal thigh group were used for I.M. injections. For I.V. test drug administration, the cephalic, femoral (III) and auricular (V) veins were used. The doses of test drugs used have been outlined in Table 5.

### **7.3. Measurements, recordings, assessments and observations**

#### ***7.3.1. Sedation and muscular relaxation (I-V)***

A summary of the variables used in assessing sedation in the original studies has been given in Table 6. In addition, times from test-drug administration to onset of sedation, recumbency and righting were recorded (I, II). Times from injection and recumbency to arousal, regaining sternal recumbency and walking were also recorded (II). Durations of profound sedation (I) and effective clinical sedation were estimated (I, II). See Table 7 for definitions of some of the variables mentioned above.

The cat's general muscular tonus was assessed by palpating, pulling and subjectively evaluating the tension in various muscle groups as; well, moderately or poorly relaxed (II, III).

**Table 6: Variables used in scoring sedation in the original studies and their score ranges**

<i>Variable</i>	<i>Study (score range in parentheses)<sup>a</sup></i>
Spontaneous posture and gait	I (0-4), II (0-6), III (0-4), IV (0-3) V (0-5)
Reaction to sound produced by hand-clap	I (0-3)
Resistance to being placed laterally recumbent	I, II (0-3)
Resistance to being placed dorsally recumbent	V (0-3)
Resistance to hindlimb stretching without pinching	II, III (0-3)
Resistance to stretching knee joint	II (0-2) III (0-3)
Degree of resistance to manipulations (handling)	IV (0-2)
Degree of jaw relaxation	I (0-3), II (0-2), III (0-3), V (0-1)
Palpebral reflex	V (0-2)
Limb withdrawal in response to light interdigital pad pinching	I (0-3), V (0-2)
Maximum possible total sedation score	I (16), II (19), III (16), IV (5), V (13)

<sup>a</sup>For each variable studied, it was assumed that the smaller the numerical value of the score, the less sedated the animal was.

**Table 7: Definition of some variables used to characterize sedation in Study I and II**

<i>Variable</i>	<i>Definition</i>
Onset of clinical sedation*	moment when the cat's eyes ceased to actively follow movement of objects
Onset of lateral recumbency	moment after test drug administration when cat began to be laterally recumbent
Arousal time	first time after lateral recumbency when repeated spontaneous body movements reappeared
Righting time	first time when cat managed to lift its head without assistance
Regaining sternal recumbency	first time when cat managed to recover sternal recumbency
Walking time	time when cat was seen taking its first step either spontaneously or after agitation
Duration of profound sedation	period from start of lateral recumbency to arousal or period over which cat obtained a sedation score of > 85% of the maximum possible score
Duration of effective clinical sedation	period over which cat obtained > 30% of the maximum possible score

\* onset of clinical sedation was tested by performing hand-waves in front of the cat's face at about 30-sec intervals from drug administration until the cat ceased to move its head from side to side in response to the hand movements.

### 7.3.2. Antinociception/analgesia and degree of restlessness (II-IV)

The extent of analgesia was assessed from variables summarized in Table 8.

Vocalization, limb movement, tail twitching, muscular fasciculation or the exhibition of any other escape behaviour were considered to be responses to nociceptive stimuli.

**Table 8: Variables used in assessing antinociception/analgesia in the original studies**

<i>Variable</i>	<i>Score range<sup>b</sup></i>	<i>Study</i>
Cat's nociceptive response to ear pinch	0-5	III
Cat's nociceptive response to tail pinch	0-5	II
Cat's nociceptive response to interdigital pad pinch	0-5	II
Cat's nociceptive response to tail clamp	0-9	II, III
Cat's nociceptive response to skin clamp	0-9	II, III
Vocalization	0-2	IV
Reaction in eyes, limb movement or other avoidance behaviour	0-3	IV

<sup>b</sup>For each variable studied, it was assumed that the smaller the numerical value of the score, the lower the degree of antinociception/analgesia experienced by the animal.

The degree of restlessness (scores in parentheses), assessed subjectively in Study IV by the same observer who was blinded to the treatment used, was scored as follows: very restless (3), restless (2), slightly restless (1) or not restless (0). Frequent rubbing of head against cage, attempts to reach operation site with mouth, attempts to remove collar from head and similar behaviours were considered to be restlessness.

### 7.3.3. Heart and respiratory rates and rectal temperature (I-V)

At each time point studied, heart rate was measured with a stethoscope over a 30-second time period. The value obtained was then doubled to get the rate per minute. Rate of respiration was similarly counted by observing rib movements over a 30-minute time period and the value obtained, doubled to get the rate per minute. Rectal temperature was

measured with a digital thermometer. The experiments were carried out at room temperatures ranging from 19°C to 22°C in all studies.

#### **7.4. Laboratory analyses**

##### ***7.4.1. Serum and CSF drug concentrations (I, III, V)***

Blood samples (2-3 ml each) were collected from the cephalic, femoral or external jugular vein via a cannula (I, II) and the heart via puncture (V) into plain tubes, and serum was separated by refrigerated centrifugation. CSF (1-2 ml) was collected from the atlanto-occipital foramen into EDTA tubes using a 21-gauge needle. The serum (I, III, V) and CSF (V) samples were stored at -18°C until analysed in duplicate for MED (I, III, V) or DEX (III) concentrations by capillary gas chromatography with negative ion chemical ionization mass spectrometry (Vuorilehto et al. 1989).

##### ***7.4.2. Plasma cortisol, glucose and albumin concentrations (V)***

Plasma was separated from the blood samples (3 ml each) collected by puncture from the auricular artery into pre-chilled EDTA tubes by refrigerated centrifugation, frozen within 30 min of collection and stored at -18°C until analysed. Plasma cortisol concentration was analysed using a commercial [<sup>125</sup>I] radioimmunoassay kit (Farnos RIA Cortisol, Farnos Group Ltd, Finland). Plasma glucose and albumin concentrations were determined using standard laboratory techniques.

#### **7.5. Statistical analyses**

Data were analysed using ANOVA (I-IV), Friedman two-way analysis by ranks (II, III), Kruskal-Wallis one-way analysis by ranks (IV), Wilcoxon signed-rank test (I-IV), Mann-Whitney U-test (IV), Spearman rank correlations (I), Pearson's correlation (V) and Student's t-test (I, V). Statistical significance was set at P<0.05. Areas under the

concentration versus time and sedation versus time curves were calculated with the trapezoidal rule (I).

## 8. RESULTS

### 8.1. Sedation and muscular relaxation (I-V)

Following the administration of 50-200  $\mu\text{g}/\text{kg}$  MED (I.M.) in cats, signs of sedation appeared 2-11 min and recumbency 4-17 min after drug administration. Onset of sedation and lateral recumbency occurred more rapidly after I.M. than oral administration of the same dose of drug. DEX at half the dose of MED induced similar effects. Even though no clear dose-dependence was present in the onset of sedation and recumbency, high doses tended to induce more rapid onset of sedation and recumbency than low doses (I, II).

Intramuscular MED 50-200  $\mu\text{g}/\text{kg}$  dose-dependently induced about 25-80 min of profound sedation and about 2-4 hrs of effective clinical sedation in cats. Righting time was dose-dependent, occurring approximately 45-150 min after the onset of lateral recumbency. The dose-dependence, however, reached a ceiling point since duration of effective clinical sedation was identical between the two highest doses used (150 and 200  $\mu\text{g}/\text{kg}$ ). DEX at half the dose of MED induced similar effects. The durations of profound and effective clinical sedation did not differ between the oral and I.M. routes (see Table 9 for definition of variables) (I, II). At an I.M dose of 100  $\mu\text{g}/\text{kg}$ , MED induced a longer duration of effective clinical sedation (about 230 min) than DEX 50  $\mu\text{g}/\text{kg}$  I.M. (about 202 min), but proceeding from 100 to 150  $\mu\text{g}/\text{kg}$  MED (or from 50 to 75  $\mu\text{g}/\text{kg}$  DEX), DEX increased effective clinical sedation better (by about 57 min) than MED (about 14 min). The 90% confidence interval of the ratio of means (DEX/MED) for effective clinical sedation were within the interval 0.8-1.2 at each dose level studied (II).

MED and DEX (infused at half the rate of MED) induced similar levels of sedation at all stages of the three-step continuous I.V. infusion of these drugs in cats (III). Sedation induced by 15  $\mu\text{g}/\text{kg}$  MED (I.M.), administered after ovariohysterectomy in cats, was mild and similar to sedation induced by 0.1 mg/kg butorphanol (I.M.). Sedation induced by MED (15  $\mu\text{g}/\text{kg}$ , I.M.) or butorphanol (0.1 mg/kg, I.M.) was, however, more intense than that induced by placebo (IV). MED induced effective muscular relaxation in cats

that was similar to DEX (administered at half the concentration of MED) following both I.M. and I.V. administrations (II, III).

### **8.2. Antinociception/analgesia and degree of restlessness (II-IV)**

Analgesia in cats increased dose-dependently following the administration of MED or DEX in Studies II and III. MED had similar analgesic effects as DEX.

For at least 2 hrs postoperatively, cats that had received 15 µg/kg MED (I.M.), 0.1 mg/kg butorphanol (I.M.) or saline placebo after ovariohysterectomy experienced different degrees of pain. Those that had received butorphanol had the best pain relief, whereas those receiving placebo had the worst (IV). For at least 2 hrs postoperatively, restlessness increased in cats that had received placebo but was prevented in those that had received 15 µg/kg MED (I.M.) or 0.1 mg/kg butorphanol (I.M.) after ovariohysterectomy (IV).

### **8.3. Heart and respiratory rates and rectal temperature (I-V)**

MED and DEX reduced heart rate in cats and rabbits at all doses studied (I-V). Proceeding from 100 to 150 µg/kg (I.M. MED) or 50 to 75 µg/kg (I.M. DEX) in cats, DEX caused a further decrease in heart rate but MED did not (II).

Both MED and DEX decreased the rate of respiration in cats and rabbits, but values remained within physiological limits (I-V). There was no clear significant dose-dependence in this effect. MED and DEX had similar effects on the rate of respiration (II, III). The extent to which MED decreased the rate of respiration did not differ between the oral and I.M. routes of drug administration (I). At 60 and 90 min after the administration of 15 µg/kg MED (I.M.) or 0.1 mg/kg butorphanol (I.M.) to cats which had undergone ovariohysterectomy, respiratory rates were lower in those that had received butorphanol than those receiving MED, but rates remained within physiological limits (IV).

Rectal temperature decreased after the administration of MED or DEX in cats (I, II, IV).

#### 8.4. Serum and CSF drug concentrations (I, III, V)

Time ( $t_{\max}$ ) when the peak serum concentration was reached appeared earlier after I.M. ( $21.57 \pm 10.05$  min) than after oral ( $43.57 \pm 14.35$  min) administration of MED in cats ( $p = 0.022$ ). Peak serum concentration ( $C_{\max}$ ) reached following the administration of 200  $\mu\text{g}/\text{kg}$  MED (I.M.) was  $78.04 \pm 38.10$  ng/ml, and this was not significantly different from values obtained following oral ( $149 \pm 228.57$  ng/ml) administration ( $p = 0.933$ ). The area under the drug concentration-time curve (AUC-c) was not significantly different between the oral and I.M. routes. The greater the extent of salivation, the smaller the AUC-c ( $r = -0.926$ ;  $p = 0.038$ ). One cat that did not vomit or salivate had higher AUC-c and  $C_{\max}$  values than the corresponding I.M. values. For both oral and I.M. administrations, the bigger the area under the sedation-time curve (AUC-s), the bigger the AUC-c (oral:  $r = 0.821$ ,  $p = 0.044$ ; I.M.:  $r = 0.857$ ,  $p = 0.036$ ) (I).

Serum drug concentration increased dose-dependently after a three-step I.V. infusion of MED or DEX in cats. The median values were 14.5 (interquartile range = 2.0) ng/ml for MED and 9.2 (interquartile range = 3.7) ng/ml for DEX at the end of infusion step 1; 77.7 (interquartile range = 36.6) ng/ml for MED and 51.3 (interquartile range = 0.8) ng/ml for DEX at the end of step 2; and 455.0 (interquartile range = 62.0) ng/ml for MED and 228.5 (interquartile range = 35.0) ng/ml for DEX at the end of step 3 (see Table 7 for doses used). Even though the infusion rate of DEX used at each step was half the corresponding rate of MED, the serum DEX concentration did not differ significantly from either the MED concentration or 50% of the MED concentration. For both MED and DEX, sedation increased as serum drug concentration increased up to at least 77.7 ng/ml (median) MED or 51.3 ng/ml (median) DEX. At 455 ng/ml (median) (MED) or 228 ng/ml (median) (DEX), sedation was less profound than at lower serum drug concentrations (III).

Following the administration of 100  $\mu\text{g}/\text{kg}$  MED (I.V.) in rabbits, the serum drug concentration reached was  $52.0 \pm 40.5$  ng/ml and CSF drug concentration  $6.6 \pm 3.3$  ng/ml; thus, the MED concentration detected in the CSF was  $17 \pm 13\%$  of the serum

value (V). The higher the CSF drug concentration reached, the lower the level of sedation attained ( $r = -0.500$ ,  $p = 0.029$ ). However, the higher the serum drug concentration, the higher the CSF drug concentration reached ( $r = 0.598$ ,  $p = 0.007$ ).

### **8.5. Plasma cortisol, glucose and albumin concentrations (V)**

The higher the plasma cortisol or glucose concentration prior to the administration of 100  $\mu\text{g/kg}$  MED (I.V.) in rabbits, the lower the concentration of MED detected in serum after drug administration (for cortisol:  $r = -0.462$ ,  $p = 0.031$ ; for glucose:  $r = -0.448$ ,  $p = 0.037$ ). Plasma cortisol, glucose and albumin concentrations prior to MED administration were not related to the concentration of MED detected in the CSF of rabbits (V).

## **9. DISCUSSION**

### **9.1. Sedation, antinociception/analgesia and restlessness**

#### ***9.1.1. Sedation***

##### ***9.1.1.1. Oral administration (I)***

Spraying MED into the mouth proved effective for sedating cats. The drug may have been absorbed from the oral mucosa, thereby escaping the hepatic first-pass effect. This is consistent with an earlier report that MED sprayed onto the buccal mucous membrane beneath the tongue in cats produced effective sedation (Brearley, 1994). Similarly, either detomidine or medetomidine in combination with ketamine has been administered orally to induce sedation in cats (Wetzel and Ramsay, 1998; Grove and Ramsay, 2000). Detomidine has also been administered sublingually or placed in the mouth to induce sedation in horses (Malone and Clarke, 1993; Ramsay et al., 2002). The oral route has been used effectively to administer dexmedetomidine to dogs (Proctor et al., 1991; 1992; Kersten et al., 1993; Devcic et al., 1994) and humans (Anttila et al., 2003). This non-invasive transmucosal means of delivering MED can be useful for sedating wild or uncooperative cats to prevent injury to attendant personnel and/or the cat. It can also be utilized for sedating cats prior to transportation. We have also demonstrated the benefits of postoperative administration of MED to cats (IV). Repeated injections can, however, be time-consuming and expensive for the cat owner. This non-invasive transmucosal method may therefore open future possibilities for cat owners to administer MED to their pets in times of need. One limitation is, however, that accurate dosing can be difficult to achieve since some drug may be lost through salivation or vomiting (and probably through hepatic first-pass metabolism as well). The cats did not appear to like the taste of the commercial MED used; therefore, improving the taste of MED may help to reduce salivation and increase systemic drug availability following oral administration. It is worth mentioning that the current commercial form of MED can be potentially dangerous in the possession of cat owners since accidents can easily occur through inappropriate

handling or usage. For a practical approach to involving cat owners in MED administration therefore, a more suitable form of the drug or a delivery system may have to be developed (the form of the drug or a delivery system that would reduce the risk of accidents and address adequately, the issue of safety).

MED causes peripheral vasoconstriction through the activation of postsynaptic  $\alpha_2$ -adrenoceptors on blood vessels (Savola et al., 1986). After being sprayed into the mouth of the cat at a high concentration, the drug probably caused constriction of blood vessels in the oral mucosa, thereby slowing absorption and clearance from the site of administration. MED, after its I.M. administration, may have been subjected to a similar fate, but to a lesser extent, since the diameters of the blood vessels in the muscles were larger. This may explain the significant difference in  $t_{max}$  between the oral and I.M. routes. The possibility that part of the drug was swallowed and subsequently absorbed through the stomach or intestines, leading to a delay in the  $t_{max}$  after oral administration, must not be overlooked. The oral mucosa has a rich supply of blood capillaries such that if MED was absorbed through it, the expectation would be that in the absence of vomiting or extensive salivation, systemic drug availability would be comparable with, or even better than that achieved after I.M. administration, which indeed was the case here. Similarly,  $t_{max}$  was delayed after detomidine had been sprayed into the mouth of the horse ( $C_{max}$  was reached at about 75 min post-drug administration) (Ramsay et al., 2002).

The drug may have remained in the oral cavity under the folds of the mucosal membrane or become mixed with saliva, which served as a reservoir for the drug after oral administration for that relatively long period while it underwent absorption. The situation resembles a slow continuous infusion process, whereby the drug over a given period of time continuously moves from “the reservoir in the mouth” into the bloodstream. Considering the proximity of the capillaries in the oral cavity to the external jugular vein and the possible continuous flow of the drug into the latter, blood sampled from this vein may have contained a higher concentration of the drug than the general circulation following oral administration. This could have introduced some errors in interpreting the

measured concentrations and given a false picture about the oral:I.M. concentration ratios.

#### ***9.1.1.2. Dose response (I - III)***

Rapid onset of sedation with MED (I.M.) or DEX (I.M.) in cats suggests that the drugs are rapidly absorbed following I.M. administration. This is consistent with an earlier report by Salonen (1989). Onset of sedation has been reported to be more rapid after I.M. than sublingual administration of detomidine in horses (Malone and Clarke, 1993) as found in cats in our study. Onset of sedation was not dose-dependent for MED or DEX after I.M. administration. It is possible that relatively small amounts of these drugs or few drug-receptor interactions are required to initiate sedation. If this is the case, then the doses of MED or DEX used probably provided adequate brain concentrations to fulfill these requirements such that within the limits of the experimental procedures used, differences in onset of sedation between doses were not statistically significant. High levels of MED have been detected in the rat brain already at 5 min after I.M. dosing (Salonen, 1989).

The sedative effect of MED or DEX in cats was dose-dependent. This dose-dependence reached a ceiling point. As dosing approached this ceiling point, sedation tended to wane in duration and intensity, and at doses beyond the ceiling point, sedation showed a tendency to be decreased in depth. The exact dose point or serum drug concentration at which this ceiling effect occurred was not established. Up to MED 100 µg/kg or DEX 50 µg/kg, sedation still appeared to be strongly dose-dependent in duration and intensity. By MED 150 µg/kg or DEX 75 µg/kg, the dose-dependence persisted but weakly. Since the duration of effective clinical sedation was identical for MED 150 µg/kg (I.M.)(II) and MED 200 µg/kg (I.M.) (I), one could say that by 200 µg/kg MED, the dose-dependence of MED had further weakened or had begun to cease. At least by the time serum concentrations reached MED 455 ng/ml or DEX 228 ng/ml the depth of sedation had decreased.

No evidence as to why this occurred was found but possibly as the concentration of the drug increased, more  $\alpha_2$ -adrenoceptor sites preferentially got occupied (dose-dependence stage). As the population of unoccupied  $\alpha_2$ -adrenoceptor sites approached a point of complete depletion, a further increase in the concentration of the drug probably led to a simultaneous occupation of unoccupied  $\alpha_2$ - and  $\alpha_1$ -adrenoceptor sites in identical proportions (approaching a ceiling point) until available  $\alpha_2$  sites were completely depleted (ceiling point). An increase in the concentration of the drug beyond this point probably led to the occupation of  $\alpha_1$  sites, which in turn caused a further decrease in sedation depth (this situation resembled sedation reversal and has therefore been referred to elsewhere in this thesis as the reversal stage). MED and DEX are known not to be completely devoid of affinity for  $\alpha_1$ -adrenoceptors (Virtanen et al., 1988; Schwinn et al., 1991) and activation of  $\alpha_1$ -adrenoceptors has been demonstrated to induce arousal, restlessness, increased locomotor activity (Monti, 1982) and increased vigilance (Monti, 1982; Puumala et al., 1997). Similarly, central  $\alpha_1$ -adrenoceptor stimulation attenuated the  $\alpha_2$ -mediated sedative/hypnotic effect of DEX (Guo et al., 1991; Schwinn et al., 1991) at high but not low doses of the drug (Doze et al., 1989). It has therefore been proposed that low doses of DEX should be used to maximize its sedative/hypnotic effects (Schwinn et al., 1991). Alpha-2A-receptors have been found in high densities in the LC (Wang et al., 1996), where their activation leads to sedation (Nacif-Coelho et al., 1994; Hunter et al., 1997; Lakhiani et al., 1997). Alpha-1-receptors also exist in the LC (Sinha et al., 1984; Osborne et al., 2002) and function to suppress  $\alpha_2$ -receptor-activated GIRK conductance (Osborne et al., 2002). Activation of some  $\alpha_1$ -receptors outside the LC may also cause functional antagonism of  $\alpha_2$ -mediated sedative/hypnotic responses (Correa-Sales et al., 1992). All of these examples together seem to support  $\alpha_1$ -adrenoceptor involvement in the attenuation of sedation, as observed in the present study. The l-isomer in MED may have contributed to attenuating MED-induced sedation (see below), but since DEX which lacks the l-isomer, behaved in a similar manner, the  $\alpha_1$ -receptor involvement hypothesis seems more likely. The sedative effects of MED and DEX have also been reported to be dose-dependent and to display a ceiling effect in animals (Vainio et al., 1989; Kuusela et al., 2000).

Even though the activation of  $\alpha_1$ -adrenoceptors at high drug concentrations was suspected to be the cause of the decrease in sedation, the possibility that  $\alpha_2$ -adrenoceptor desensitization following continuous exposure to DEX or MED (III) contributed should not be overlooked. Desensitization or adaptation to chemical signals can result from a gradual decrease in the number of specific cell-surface receptor proteins (generally takes hours), a rapid inactivation of such receptors (can occur in minutes), a change in the proteins involved in transducing the signal following receptor activation (usually occurs with an intermediate time course) or other ways (Alberts et al., 1994). The pertussis toxin-sensitive G-protein has been reported to become uncoupled from the  $\alpha_2$ -receptor in the LC of  $\alpha_2$ -tolerant rats (Reid et al., 1994). Additionally, chronic administration of DEX (7 days of continuous S.C. administration via osmotic minipumps) desensitized rats to the hypnotic properties of the drug (Reid et al., 1994; Hayashi et al., 1995) through a decrease in end-organ responsiveness (Reid et al., 1994).

#### ***9.1.1.3. MED versus DEX (II, III)***

The reasons for the slight differences between the effective clinical sedation induced by MED (100  $\mu\text{g}/\text{kg}$ ) and DEX (50  $\mu\text{g}/\text{kg}$ ) and also while proceeding from MED 100 to 150  $\mu\text{g}/\text{kg}$  or DEX 50 to 75  $\mu\text{g}/\text{kg}$  remains obscure. It is possible that as the concentration of MED increased, the l-isomer in MED acted as a positive agonist, adding some sedative effect to the drug, and as the concentration increased further, the l-isomer then acted as an inverse (negative) agonist, blocking the alpha-2-receptor sites and depriving the pharmacologically active d-isomer in MED of free alpha-2 sites with which to interact. In this situation, MED, which contains the l-isomer, would be expected to exhibit limited sedative effect as compared with DEX which lacks the l-isomer. LEV behaved as a protean agonist overall (Kenakin, 2001), consistent with a report by Jansson and others (1998). Similarly, LEV at high concentrations showed weak positive alpha-2-agonistic properties under some conditions (Savola and Virtanen, 1991; Jansson et al., 1994a; 1994b; 1995) and alpha-2-antagonistic (MacDonald et al., 1991) or inverse agonistic (Jansson et al., 1998) properties in others. A high dose of LEV has also reduced the

sedative effects of DEX in dogs (Kuusela et al., 2001 b). In addition, LEV has shown some binding (albeit slight) to alpha-2-receptors (MacDonald et al., 1991).

It is also possible that at very high doses the l-isomer in MED contributed some alpha-1-related antisedative effect to MED, making it less potent than DEX.

In this study, the sedative effect of MED and DEX (administered at half the concentration of MED) in cats tended to be identical. Pharmacological activities of MED in cats may therefore be due predominantly to the dextro-rotatory isomer. This is consistent with earlier findings in other animal species (MacDonald et al., 1991; Savola and Virtanen, 1991; Schmeling et al., 1991; Kuusela et al., 2001a). The small difference noted in the duration of effective clinical sedation was such that the effects of the two drugs could be considered as being therapeutically equivalent and the difference to have little or no clinical relevance. A statistically significant difference may exist between treatments, but this may be of no clinical relevance and correspond to practical equivalence (Jones et al., 1996).

Results from this study suggest that although the l-isomer of MED may contribute little or no sedative effect to the drug, it might contribute some antisedative effects depending on its concentration. In terms of dose variations, it may be difficult to predict precisely when and to what extent the l-isomer of MED will exhibit sedative or antisedative effects. This situation may introduce some inconsistencies in the sedative effects of MED at certain doses in cats, giving DEX a therapeutic advantages over MED.

### ***9.1.2. Antinociception/analgesia (II – IV)***

At the clinically recommended doses, systemic MED (50-150 µg/kg) or DEX (25-75 µg/kg) induced rather mild analgesia in cats (II, III), which would probably only suffice for mildly painful clinical manipulations.

When a low dose of MED (15 µg/kg) was administered systemically, the drug had a tendency to prevent an increase in postoperative pain rather than actively reducing existing pain (IV). This was probably a sedation-related response, suppressing some pain-related behaviours in cats. Likewise, low doses of systemic MED (55-100 µg/kg) have been insufficient for inducing antinociception in rats, but the same doses have been adequate for suppressing highly organized pain-related behaviour (Pertovaara et al., 1990). In humans, low doses of systemic MED similarly attenuated the affective-motivational component of experimental pain while the same doses failed to suppress the sensory-discriminatory aspects of the pain (Kauppila et al., 1991).

Synergism has been known to occur following the administration of  $\alpha_2$ -agonists together with opioids. Since cats in Study IV were anaesthetized with a MED-ketamine combination for surgery, any remaining MED in the cat's blood at the time of butorphanol administration would be expected to strengthen the effect of this opioid. It is therefore possible that at some point in Study IV comparisons were actually of MED+MED vs MED+butorphanol rather than simply MED vs butorphanol. This situation could have led to an exaggeration of butorphanol's effects.

Sedation and analgesia followed similar trends in some parts of the current study with cats (II). Possibly, part of the analgesia induced by MED or DEX was sedation-related. Agents which influence vigilance, motor reaction, autonomic reflexes and neuroendocrine functions are likely to influence subjective experiences of pain (Stenberg, 1986) making it difficult to distinguish between sedative and analgesic effects when investigating drugs possessing both properties (Vainio et al., 1989).

It is not clear why analgesia had a tendency to continue increasing while sedation decreased after certain serum drug concentrations were exceeded (III). In a similar example in rats, the analgesic effect of DEX persisted after the hypnotic response had been attenuated following chronic administration of the drug, leading the researchers to suggest that DEX requires fewer  $\alpha_2$ -adrenoceptors to elicit an analgesic response than it does to elicit a hypnotic response (Hayashi et al., 1995). Hayes and others (1986a, 1986b)

who studied different  $\alpha_1$ - and  $\alpha_2$ -agonists and -antagonists in rats and dogs, speculated that antinociception may be mediated by either  $\alpha_1$ - or  $\alpha_2$ -adrenoceptors, whereas sedation is predominantly mediated by  $\alpha_2$ -adrenoceptors. In another study with mice, however,  $\alpha_2$ -adrenoceptor stimulation increased, while  $\alpha_1$ -adrenoceptor stimulation decreased antinociception (Sebetkasai et al., 1997). These studies did not investigate the involvement of  $\alpha_1$ -adrenoceptor subtypes, although different subtypes of the receptor may have been stimulated, leading to these conclusions. The present study seems to provide some evidence that in cats, achieving analgesia with MED or DEX may be possible with little or no sedation (III). Similar views have been expressed by Heyes and others (1986a, 1986b) and Hayashi and others (1995) after studying  $\alpha_2$ -agonists in rats and dogs. This situation would be beneficial in the postoperative period, when analgesia is required but little or no sedation is needed.

The analgesic effects of MED and DEX (administered at half the concentration of MED) were similar (II, III). This suggests that the analgesic effects of MED are due predominantly to its d-isomer, i.e. the l-isomer lacks analgesic effect. In dogs, LEV has similarly been reported to be devoid of analgesic properties (Kuusela et al., 2000). Analgesia lasting longer with DEX than with MED in dogs (Kuusela et al., 2000) further suggests that the l-isomer may not only lack analgesic effect but may even shorten the duration of analgesia.

### **9.1.3. Restlessness (IV)**

Restlessness may have been an index of the discomfort that the cat experienced. Redeeming the cat from this discomfort (stress) would be helpful in speeding up postoperative recovery. Since MED and butorphanol were effective in preventing restlessness, postoperative administration of these drugs may enhance recovery in cats undergoing surgery.

## 9.2. Heart and respiratory rates and rectal temperature (I-V)

Proceeding from MED 100 to 150 µg/kg or DEX 50 to 75 µg/kg, MED reduced heart rate to a lesser extent than DEX while simultaneously inducing a shorter duration of sedation. As in the case of sedation, this difference may have been due to the l-isomer in MED acting as a protean agonist or  $\alpha_1$ -related antagonistic (see under sedation above). Since a similar subtype ( $\alpha_{2A}$ ) mediates both sedation (Hunter et al., 1997; Lakhani et al., 1997, Sallinen et al., 1997) and bradycardia (MacMillan et al., 1996; Nicholas et al., 1996; Altman et al., 1999; Zhu et al. 1999), the association observed between the two variables (sedation and reduced heart rate) was not completely unexpected. Even though the difference in heart rate was slight and may have little or no clinical relevance, attention needs to be drawn to the possibility that the presence of the l-isomer in MED may not always be a disadvantage since extensive reduction in heart rate (and possibly cardiac output and other cardiovascular variables) is usually not desirable. On the other hand, if a certain level of sedation is needed, it can be achieved with a smaller dose of drug to minimize these cardiovascular effects. The l-isomer in MED may therefore play a protective role and under some circumstances confer therapeutic advantages over DEX. Dogs that were premedicated with MED for propofol-isoflurane anaesthesia have been reported to have higher heart rates than those receiving DEX but this difference could be attributed to isoflurane (Kuusela et al., 2001a). In another study in dogs, Kuusela and others (2001b) reported that a combination of high doses of LEV with DEX caused further reduction in heart rate. It seems therefore that the l-isomer in MED can cause either an increase or a decrease in heart rate depending on its concentration (whether it acts as a positive agonist or an antagonist/inverse agonist) and probably some other conditions.

Decreases in heart and respiratory rates and rectal temperature induced by MED and DEX observed here were similar to previous reports where MED was used in cats and other animal species (Stenberg et al., 1987; MacDonald et al., 1988b; Vainio, 1989; Vähä-Vahe, 1989).

### 9.3. Serum and CSF drug concentrations (III, V)

The reason for MED concentration in the CSF correlating negatively with the level of clinical sedation remains obscure. More drug molecules may have been bound to alpha-2-adrenergic receptors in the more sedated animals, leaving less (unbound) MED molecules available for the concentration analysis. DEX concentration was reported to peak in CSF 2-10 min after the end of a 60-min I.V. infusion in humans and to remain somewhat stable for at least 30 min afterwards (Talke et al., 1997). The CSF sample taken 20 min after an I.V. bolus dose of MED in the present study may therefore have been close to the peak concentration. Peak sedation has also been found to occur 10-20 min after I.V. administration of MED or DEX in dogs (Kuusela et al., 2000). Scoring of sedation 15 min after I.V. MED administration to rabbits in Study V may have similarly represented or been close to the moment of peak sedation.

MED concentration in CSF was  $17 \pm 13\%$  (range 6-58) of serum concentration 20 min after an I.V. bolus administration. In humans, DEX concentration in CSF has been found to be  $4 \pm 1\%$  of plasma concentration at the end of a 60-min I.V. infusion (Talke et al., 1997). In rats, the maximum concentration in brain tissue was five times the corresponding plasma concentration 20 min after drug administration (Salonen, 1989). These findings suggest that the concentration in brain tissue is probably much higher than in CSF.

If the metabolism of DEX is identical to that of MED, after administering DEX at half the concentration of MED, the serum drug concentrations would be expected to exist in a ratio of 1:2 (DEX: MED). Since the serum drug concentrations did not differ significantly between DEX and MED, the rate at which the two drugs are metabolised in cats may not be the same. It should, however, be noted that differences between serum DEX and 0.5 serum MED concentrations were not statistically significant either. For 5 out of the 6 cats serum DEX concentration was slightly more than half the value for MED (III), indicating that a tendency existed for DEX to be less rapidly metabolised than MED. A large dose of MED has been reported to cause haemodynamic changes, resulting in decreased

hepatic circulation and subsequent slowing of drug metabolism in dogs (Salonen et al., 1995). Antagonism with atipamezole has also been shown to restore hepatic blood flow, with an increased elimination of MED (Salonen et al., 1995). Similarly, DEX reduced heart rate (and possibly cardiac output and other haemodynamic determinants of hepatic blood flow) more than MED at some point in this study and some antagonism or inverse agonism was possibly encountered with the presence of the l-isomer in MED (see above). In another study with dogs, the clearance of LEV (administered I.V. at 20 or 10 µg/kg) was reported to be more rapid than MED (administered I.V. at 40 µg/kg) or DEX (administered I.V. at 10 or 20 µg/kg) (Kuusela et al., 2000). This report is in agreement with findings of the current study because at low concentrations, it would be expected that LEV will exhibit zero or negligible pharmacological activity (i.e. haemodynamic changes due to LEV would be expected to be nil or negligible). In such a situation, the clearance of MED and DEX administered at equipotent doses will be identical since the two drugs are expected to cause similar degrees of reduced heart rate (and reduced hepatic blood flow for that matter), whereas the clearance of LEV will be comparatively more rapid since it is not retarded by a reduced heart rate. This expectation was indeed confirmed in Kuusela and others' (2000) work.

#### **9.4. Serum MED and plasma cortisol or glucose concentrations (V)**

Since plasma cortisol and glucose concentrations correlated negatively with serum MED concentration, it is possible that stress – as indicated by these parameters– may have some effect on the distribution or metabolism of MED.

## 10. CONCLUSIONS

- 1) An oral-mucosal application of MED is effective for sedating cats. When salivation and vomiting are minimal or do not occur, the amount of MED which becomes systemically available to the cat and the corresponding extent of sedation are comparable with those after I.M. administration, although the maximum blood concentration and clinical sedation are reached later after oral dosing than after an I.M. injection.
- 2) Both MED and DEX induce dose-dependent sedation and analgesia in cats that reach ceiling points beyond which sedation may be decreased. An equivalent dose of DEX (half the dose of MED) is at least as effective as MED for sedation and analgesia of cats. The sedative and analgesic effects of MED in cats are mediated predominantly via its dextro-rotatory isomer. The presence of the l-isomer in MED may not always be of therapeutic disadvantage.
- 3) At least in cats anaesthetised with MED-ketamine combination for surgery, postoperative administration of MED (systemic) relieves acute postoperative pain. MED is not, however, as potent as butorphanol, although the two drugs (at low doses) induce mild and identical levels of sedation.
- 4) Serum concentration of MED may predict the concentration of MED in the CSF of rabbits. The concentration of MED in the CSF does not in turn necessarily predict the level of sedation.

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