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Clonidine in paediatric anaesthesia:

Pharmacokinetic and pharmacodynamic aspects.

Henrik TG Bergendahl

Stockholm 2002

to my wonderful life companion Birgitta and her fantastic children
   Johannes and Clara and our beloved children Olle and Anna.

- to my parents, my sister and my brothers.

- to Professor Allan Ågren.

Dissertation quote:

"Life is what´s happening to you while you are busy making other plans"

John Lennon

ABSTRACT

Clonidine in paediatric anaesthesia: Pharmacokinetic and pharmacodynamic aspects.
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Clonidine is a mixed alpha-2/alpha-1 adrenoceptor agonist. It reduces sympathetic and increases parasympathetic tone which results in a lowering of the baseline blood pressure and heart rate. Descending postjunctional noradrenergic antinociceptive pathways originating in the brainstem are believed to contribute to pain control of both nociceptive and neuropathic origin after clonidine challenge. The sedative effect of clonidine is due to alpha-2 adrenoceptor stimulation in the locus coeruleus.

In adults, oral clonidine provides preoperative sedation, increases perioperative haemodynamic stability, reduces the requirements of volatile anaesthetic requirements, and attenuates the stress response secondary to intubation. A pure analgesic effect is seen after both systemic and neuraxial administration.

In paediatric anaesthesia similar beneficial effects have been observed. To provide safe and effective use of clonidine in children further studies delineating its specific pharmacokinetic and haemodynamic characteristics are needed, despite its recently increased clinical use. Randomised controlled trials comparing the clinical use of clonidine as a premedicant drug to the currently widely used premedicant gold standard represented by midazolam are warranted.

The primary aims of this dissertation were to describe the pharmacokinetics after different routes of administrations and delineate the intraoperative haemodynamic profile. The magnitude of the stress-response caused by endotracheal intubation with special emphasis on the Neuropeptide Y response was compared after premedication with low-dose clonidine and midazolam. The postoperative analgesic and sedative effects of clonidine after epidural co-administration together with bupivacaine has also been evaluated. The influence of epidural co-infusion of clonidine and ropivacaine on postoperative blood pressure variability was furthermore investigated. Effects on postoperative analgesia, sedation, delirium, shivering and postoperative vomiting after premedication with clonidine and midazolam were compared.

Clonidine analysis was made by radioimmunoassay. NPY was analysed with a competitive radioimmunoassay. Postoperative analgesia was assessed by Objective Pain Scale and sedation was assessed by the Vancouver Sedative Recovery Scale. A new statistical procedure for calculations of bioavailability from two independent populations was introduced. Parental preferences were assessed using a written questionnaire.

In total 238 children, age 1-10 years, were included in seven different studies. The haemodynamic response after clonidine administration was moderate and should be well tolerated in otherwise healthy children. Epidural clonidine improves blood pressure stability by reducing blood pressure variability. The pharmacokinetic profile after intravenous, rectal, and epidural administration were similar to that reported in adults. We therefore conclude that there are no pharmacokinetic or haemodynamic aspects contraindicating further use of clonidine in paediatric anaesthesia.

The stress response after endotracheal intubation is of only moderate magnitude, as indicated by the lack of NPY release, and is not attenuated by low dose of clonidine. Rectal administration of clonidine was associated with a significant reduction of pain scores in the early postoperative period following adeno-tonsillectomy when compared to rectal midazolam. The analgesic effect seen after epidural and rectal clonidine cannot be explained by residual sedation alone. The use of clonidine is also associated with slightly increased sedation ratings during the first 24 postoperative hours compared to midazolam. However, this observation is in agreement with the unequivocal parental preference of a calm and sedated child during the early post-operative time period.

Based on our own results, as well as data published by other research groups, we conclude that clonidine represents a useful pharmacological alternative in paediatric anaesthesia.

Key words: Alpha-2 adreoceptor agonists, anaesthesia, analgesia, bioavailability, clonidine, confusion, dose response, epidural, haemodynamics, intubation tracheal, midazolam, neuropeptide Y, paediatric, pharmacokinetic, postoperative, postoperative vomiting, premedication, sedation, shivering, variability.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Klonidin och barnanestesi: Farmakologiska och kliniska aspekter.

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Klonidin (Catapressan[R]) introducerades på 1960-talet som ett blodtryckssänkande läkemedel men används idag främst vid narkotika-, alkohol- och nikotinavvänjning. Farmakologiskt och kliniskt är klonidin väldokumenterat hos vuxna men fortfarande saknas väsentliga data i dessa avseenden för barn.

Klonidinets lugnande, ångestdämpande och smärtstillande egenskaper liksom stabilisering av puls och blodtryck samt dämpande effekt av stressvaret vid kirurgi är några av de positiva egenskaper som har beskrivits i samband med narkos och operation hos vuxna.

Trots de positiva erfarenheterna av klonidinanvändning i samband med narkos av vuxna patienter dröjde det till början av 1990-talet innan klonidin började utforskas för användning inom barnnarkos. I likhet med erfarenheten på vuxna har man kunnat visa att klonidin givet till barn i samband med narkos och kirurgi leder till en rad positiva effekter så som allmänt lugnande effekt, minskat stressvar vid kirurgisk stimulering samt minskat behovet av narkosläkemedel. Tillägg av klonidin till olika bedövningsformer leder också till att den smärtstillande effekten av bedövningen förlängs och fördjupas. Klonidin har även visat sig kunna minska illamående, kräkning, frossbrytningar och förvirring efter narkos hos barn.

Den huvudsakliga målsättningen med detta avhandlingsarbete var att kartlägga klonidinets farmakologiska egenskaperna i samband med narkos och kirurgi på barn i åldern 1-10 år.

Ytterligare mål var att försöka bestämma den optimala dosen i samband med narkos samt att registrera eventuella biverkningar. En viktig del var också att utvärdera klonidinets kliniska effekter jämfört med midazolam, vilket för närvarande utgör standard alternativet för premedicinering till barn inför narkos.

I de sju vetenskapliga arbeten som ingår i avhandlingsarbetet har ingen allvarlig påverkan på cirkulationen kunnat påvisas. Tvärtom har en stabilisering av blodtrycket efter tillägg av klonidin till ryggbedövning kunnat påvisas i den postoperativa fasen. Den farmakokinetiska profilen hos barn liknar den hos vuxna och utgör således inget hinder mot ett fortsatt användande av klonidin inom barnanestesi. Givet antingen som tillägg till ryggbedövning eller i form av rektallösning, har våra studier visat att klonidin har både lugnande och smärtstillande egenskaper. Den lugnande effekten efter rektallösningen sitter i under cirka 24 timmar. Klonidinets långverkande lugnande effekt uppfattas dock som positiv av 75 % av barnens föräldrar.

Baserat på våra egna forskningsresultat, sammantagna med forskningsresultat från andra forskningsgrupper, anser vi att klonidin utgör ett värdefullt och användbart farmakologiskt alternativ inom barnanestesi.

- LIST OF PAPERS

This thesis is based upon the following papers, referred to by the Roman numerals I-VII.

I.   Lönnqvist PA, **Bergendahl H**. Pharmacokinetics and haemodynamic response after an intravenous bolus injection of clonidine in children. Paediatric Anaesthesia 1993; 3: 359-364.

II.   Lönnqvist PA, **Bergendahl HTG**, Eksborg S. Pharmacokinetics of clonidine after rectal administration in children. Anesthesiology 1994; 81: 1097-1101.

III.   **Bergendahl HTG**, Eksborg S, Lönnqvist PA. Low-dose intravenous clonidine in children: plasma concentrations and haemodynamic response. Acta Anaesthesiologica Scandinavica 1997; 41: 381-384.

IV.   Ivani G, **Bergendahl HTG**, Lampugnani E, Eksborg S, Jasonni V, Palm C, Mattioli G, Podesta E, Famularo A, Lönnqvist PA. Plasma levels of clonidine following epidural bolus injection in children. Acta Anaesthesiologica Scandinavica 1998; 42: 306-311.

V.   **Bergendahl HTG**, Eksborg S, Kogner P, Lönnqvist PA. Neuropeptide Y response to tracheal intubation in anaesthetised children: effect of clonidine *vs.* midazolam as premedication. British Journal of Anaesthesia 1999; 82: 391-394.

VI.   **Bergendahl HTG**, De Negri P, Ivani G, Eksborg S, Lönnqvist PA. Increased postoperative blood pressure stability with continuous epidural infusion of clonidine in children. Anesthesia Analgesia 2002: accepted for publication.

VII.   **Bergendahl HTG**, Lönnqvist PA, Eksborg S. Clonidine *vs* midazolam as premedication in children undergoing adeno-tonsillectomy: A prospective randomised controlled clinical trial: Anesthesiology 2002; submitted.

ABBREVIATIONS

ADH   antidiuretic hormone

Alpha-2 alpha-2 adrenoceptor

ASA   American Society of Anesthesiologists

BSA   body surface area

CI   confidence interval

CSF   cerebrospinal fluid

EEG   electro-encephalogram

GFR   glomerular filtration rate

ICU   intensive care unit

MABP mean arterial blood pressure

MAC   minimum alveolar concentration

MAC_{TI} minimal alveolar concentration for endotracheal intubation

mcg   microgram

NA, NE noradrenaline, norepinephrine

ng   nanogram

NPY   neuropeptide Y

OPS   objective pain scale

PCA   patient controlled analgesia

PONV postoperative nausea and vomiting

POV   postoperative vomiting

SD   standard deviation

VEBL   verbal evaluation body language

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"Not poppy, nor mandragora, Nor all the drowsy syrups of the world, Shall ever medicine thee to that sweet sleep which thou owd´st yesterday."   Othello, William Shakespeare

BACKGROUND

1. A review of adreno- and imidazoline receptors

Adrenoceptors: classification and site of action

Ahlquist in 1948 was the first to classify adrenergic receptors into two main categories: alpha and beta-receptors (Ahlqvist, 1948). The functions associated with stimulation of these two different subgroups of adrenergic receptors are illustrated in Table 1.

Alpha adrenoceptor stimulation	**Beta adrenoceptor stimulation**
Vasoconstriction	Vasodilatation
Iris dilatation	Cardioacceleration
Intestinal relaxation	Increased myocardial inotropy
Intestinal sphincter contraction	Intestinal relaxation
Pilomotor contraction	Uterine relaxation
Bladder sphincter contraction	Bronchodilatation
	Glycogenolysis-Lipolysis
	Bladder relaxation.

Table 1. Adrenergic receptors and function. Guyton A, Textbook of medical physiology, W.B. Saunders Company, with permission.

Further identification of a subclass of presynaptic receptors by Paton and co-workers (Paton, 1969) led to the division of alpha-adrenoreceptors into presynaptic alpha-2 adrenoceptors and postsynaptic alpha-1 adrenoceptors (Delbarre 1973, Langer 1974). The first functional classification of alpha-2-adrenoceptors as inhibitory and alpha-1-adrenoceptors as excitatory was later modified following the demonstration of also excitatory alpha-2-adrenoceptors (Anden 1970) (Figure 1).
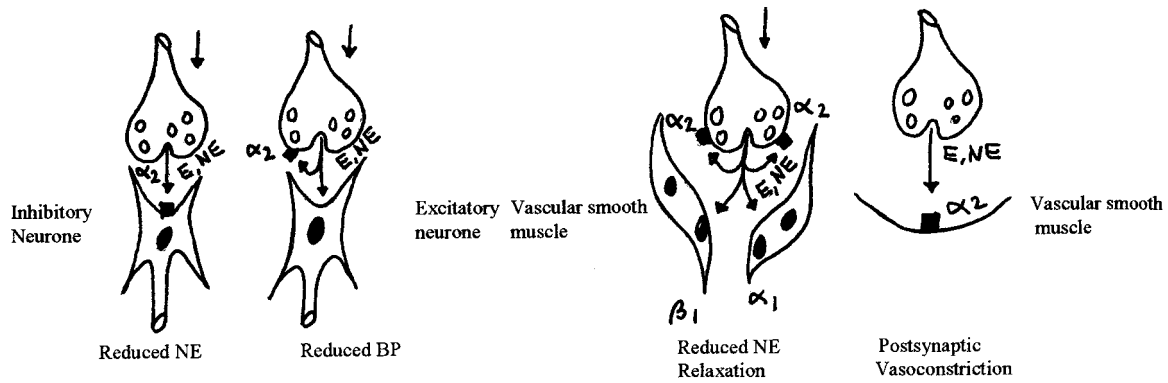
Figure 1. Inhibitory and excitatory adrenergic neurones. McCaughey W, Anaesthetic Physiology and Pharmacology, Churchill Livingstone, modified with permission.

With the development of selective antagonists such as prazosin with a high affinity for the alpha-1 adrenoceptor and yohimibine with a high affinity for the alpha-2 adrenoceptor a further pharmacological classification was made possible (Cheung 1982). This led to the identification of three different isoreceptors, alpha-2a, alpha-2b, and alpha-2c adrenoceptors, by Bylund and co-workers (Bylund 1985).

The alpha-2 adrenoceptor is a transmembrane receptor, the structure of the ligand determining whether it has agonistic or antagonistic effects on the receptor (Khan 1999). The structure and effect mechanism of the alpha-2 adrenoceptor is presented in Fig 2.
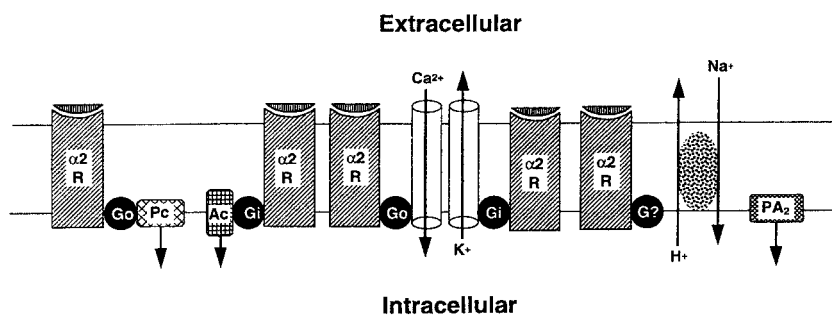
Diagrammatic representation of the structure of the alpha-2 adrenoceptor, G-proteins and possible effector mechanisms. The alpha-2 adrenoceptor agonist binds to the alpha-2 adrenoceptor ($\alpha 2$ R). This results in coupling with G-proteins due to a conformational change in the receptor protein. The alpha-2 adrenoceptor inhibits adenylyl cyclase (Ac) through the inhibitory G_i protein; transmembrane signalling is mediated by the replacement of guanosine diphosphate with guanosine triphosphate. The G_i protein also activates the outward opening of a potassium (K^+) channel, which results in hyperpolarisation. The G_o protein is coupled in an inhibitory fashion to calcium ion (Ca^{2+}) translocation and to the membrane-bound enzyme phospholipase C (Pc). The alpha-2 adrenoceptor is coupled through yet another undetermined G-protein to hydrogen (H^+) and sodium (Na^+) ion exchange and phospholipase A_2 (PA_2).

Figure 2. The structure of the alpha-2 adrenoceptor. (Khan 1999; with permission).

Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and in noradrenergic neurones in the central nervous system where they inhibit the release of noradrenaline (Langer 1974). Postsynaptic alpha-2 adrenoceptors exist in various tissues e.g. liver, pancreas, platelets, kidney, eye, and adipose tissue where they have distinct physiological functions (Kahn 1999) (Table 2).

The medullar dorsal motor complex in the brain stem has a high density of alpha-2 adrenoceptors. These receptors are likely to be associated with the central haemodynamic effects seen with alpha-2 adrenoceptor agonists (Khan 1999). The locus coeruleus, the largest noradrenergic cell group in the brain and an important modulator of wakefulness, has been indicated to be the major site for the sedative-hypnotic action of alpha-2 adrenoceptor agonists via stimulation of the alpha-2a adrenoceptor (Scheinin 1992). A high density of alpha-2 adrenoceptors has also been demonstrated in the vagus nerve (Erne-Brand 1999). The intermediolateral cell column, the substantia gelatinosa, the dorsal horn of the spinal cord, as well as primary sensory neurones all contain alpha-2 adrenoceptors (Khan 1999).

The imidazoline receptor

The alpha-2 adrenoceptor agonists clonidine, dexmedetomidine, and mivazerol, as well as catecholamines, all have an imidazoline chain in their chemical structure. In the early 1980s, Bousquet et al (Bousquet 1981) proposed the existence of non-adrenergic receptors specifically recognising imidazoline agonists or similar chemical structures.

In 1987, Ernsberger and co-workers (Ernsberger 1987) were the first to verify the existence of specific imidazoline-binding sites in the ventrolateral medulla which were insensitive to catecholamines. Two subtypes of imidazoline receptors have since been isolated. I_1 receptors are G-protein linked receptors. They have been shown to have a restricted distribution to the ventrolateral medulla in humans (Kamisaki 1990) but have also been isolated in the cat carotid body (Ernsberger 1998). I_2 receptors, which are found mainly in the mitochondrial membrane, are not G-protein linked (Regunatan 1991 A), and have not so far been identified in neuronal plasma membranes (Regunatan 1991 B). I_2 receptors are found in the liver, platelets, adipocytes, kidneys, adrenal medulla and the brain including the frontal cortex (Zonnenschein 1990, Petrusewica 1991, Diamant 1992, Lachaud- Pettiti 1991, Regunatan 1993).

Imidazoline receptor stimulation has been implicated to play a role in neuroprotection as seen in the animal models of focal lesions (Regunatan 1991 B, Laudenbach 2002). It is also

likely that imidazoline receptor stimulation is associated with the genesis of adrenaline-induced dysrhythmia under halothane anaesthesia since the imidazoline-agonist rilmenidine inhibits such dysrhythmias in dogs (Mammoto 1996). I_1-receptors have also been thought to be involved in blood pressure regulation (Kamisaki 1990).

Several endogenous ligands for imidazoline receptors have been detected, but the structure of only one, agmatine (decarboxylated arginine) is known. Agmatine is widely distributed in human tissue, bioactive, and binds to alpha-2 adrenoceptors and imidazoline receptors of all subclasses (Regunatan 1996). Considerable amounts of this endogenous ligand can be found in gastric juice where Helicobacter pylori has been shown to both form and release agmatine (Molderings 1999).

When compared to clonidine the new generation of imidazoline receptor agonists have a much higher specificity to the imidazoline receptor than to the alpha-2 adrenoceptor, which may explain the milder sedative effects of these new antihypertensive compounds (Prichard 2000) (Figure 3).
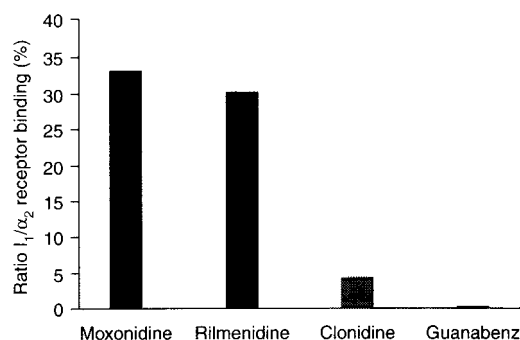

Figure 3. Relative receptor selectivity of different antihypertensive agents. (Prichard 2000; with permission).

Physiological effects mediated by stimulation of alpha-2 adrenoceptors

Alpha-2 adrenoceptor agonists have minimal effects on ventilation in therapeutic doses although respiratory depression has been described following intoxication (Olsson 1983, Anderson 1981). In adults clonidine in doses up to $300\,\text{mcg kg}^{-1}$, has been shown to result in a small reduction in resting minute ventilation and expired carbon dioxide concentration (Ooi 1991). Alpha-2 adrenoceptor agonists have no significant effect on hypercapnic or hypoxic ventilatory drive and do not potentiate the ventilatory depression caused by opioids (Baily 1991, Jarvis 1992).

Stimulation of alpha-2 adrenoceptors increase the glomerular filtration rate (Molderings 1999) and promotes both diuresis and natriuresis by decreasing the secretion of ADH and antagonising its action on renal tubules (Smyth 1985). In rodents the release of renin is inhibited (Pettinger 1987) as well as the release of atrial natriuretic factor (Chen 1989).

Salivary flow is reduced by alpha-2 adrenoceptor agonists (Watkins 1980) and colonic water and ion secretion is inhibited, explaining why diarrhoea successfully can be treated with alpha-2 adrenoceptor agonists (McArthur 1982). Activation of prejunctional alpha-2 adrenergic receptors also inhibits the vagally mediated release of gastric acid from parietal cells (Cheng 1987). However, no change in gastric pH has been observed following alpha-2 adrenoceptor stimulation in humans (Orko 1987).

Insulin release can be affected after a challenge by alpha-2 adrenoceptor agonists but this effect is not large enough to cause any clinical concern (Massara 1983). Alpha-2 adrenoceptor agonists increase the release of growth hormone (Grossman 1987) and inhibit adipose tissue lipolysis. The release of stress hormones such as ACTH and cortisol following surgery is also modified (Masal 1985).

Higher doses of alpha-2 adrenoceptor agonists (> 5 mcg kg^{-1}) stimulate platelet aggregation (Grant 1980) whereas lower doses indirectly decrease adrenaline concentrations, thus, reducing platelet aggregation. Alpha-2 adrenoceptor receptor stimulation also causes the release of nitric oxide, a potent platelet aggregation inhibitor (Radomski 1987). However, the net effect of alpha-2 adrenoceptor stimulation does not appear to cause any clinically significant effect regarding platelet function.

The physiological responses mediated by alpha-2 adrenoceptors are shown in table 2 below.

Response	Mechanism	Reference
Vasoconstriction	Postsynaptic	Ruffolo 1985
Hypotension	Central vasomotor	Bousquet 1981
Vasodilatation	EDRF	Thom 1985
Bradycardia	Baroreflex sensitivity	Harron 1985
	Decrease NE release	Reid 1977
Negative dromotropy	Vagomimetic	De Jonge 1981
Decrease ventilation	Sleeplike action	Sperry 1990
Bronchodilation	Smooth muscle ?	Lindgren 1986
Decrease saliva	Inhibit Ach release	Watkins 1980
Decrease bowel motility	Inhibit Ach release	McArthur 1982
Sedation	Increase stage I, II sleep	Dollery 1988
Anxiolysis	Decrease NE neurotransm	Scheinin 1989
Analgesia	Opioidergic mechanism	Xie 1986
	Inhibit nociceptive pathw.	Fleetwood-Walker 1985
Diuresis	Inhibit ADH release	Humphreys 1975
	Block ADH action	Smyth 1985
	Increase GFR	Strandhoy 1985
	Inhibit renin release	Smyth 1987

Table 2. Physiological responses mediated by alpha-2 adrenoceptors. (Maze 1991; modified with permission).

The role of alpha-2 adrenoceptors in heart rate and blood pressure regulation

Effects on systemic blood pressure after systemic administration

Neither the exact location nor the specific receptors responsible for the central hypotensive action of alpha-2 adrenoceptor agonists are yet known. Involvement of postsynaptic alpha-2 adrenoceptors and I_1- imidazolinereceptors in the brainstem have been suggested (Tibirica 1991) although the role of imidazoline receptors have been questioned (Guyenet 1997). The action of different antihypertensives is illustrated in Figure 4.
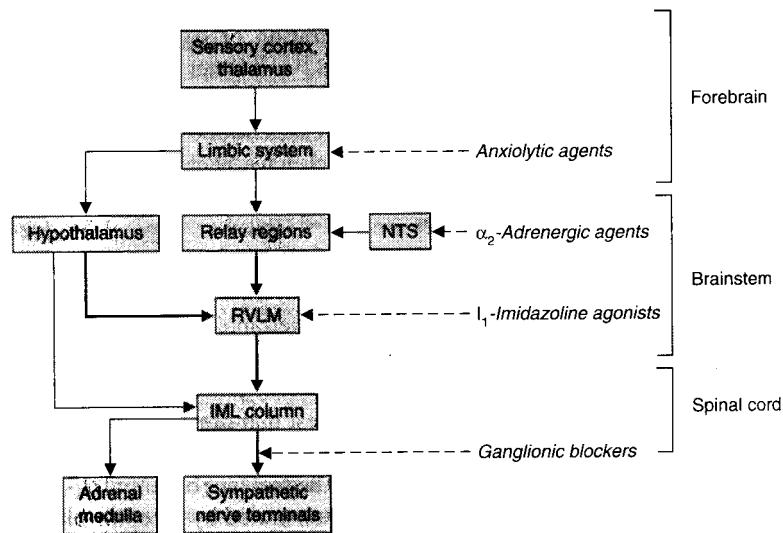
Figure 4. Mode of action of antihypertensives. (Prichard 2000; with permission).

Vascular alpha-1 and alpha-2 adrenoceptors co-exist in both arterial and venous vasculature, and are capable of mediating vasoconstriction independent of the vascular nerve supply (Ruffolo 1985). Alpha-1 adrenoceptor stimulation produces vasoconstriction by utilising intracellular calcium while the alpha-2 adrenoceptor-mediated effect is dependent on extracellular calcium (Nichols 1991). This makes the pressor response after an alpha-2 adrenoceptor agonist challenge more sensitive to calcium antagonists (Bloor 1992). Local anaesthetics also act partly by blocking calcium channels and a combination of local anaesthetics, calcium channel blockers, and alpha-2 adrenoceptor agonists could potentially pronounce a synergistic negative chronotropic and inotropic effect on the myocardium as well as a synergistic effect on the relaxation of the vasculature.

Alpha-2 adrenoceptor stimulation not only lowers the baseline blood pressure values but also lowers the set point around which arterial blood pressure is regulated (Badoer 1983). Thus, the baroreceptor reflex is not abolished but only re-set at a lower level. The alpha-2 adrenoceptor agonist clonidine is only capable of decreasing blood pressure that is dependent on sympathetic tone and, thus, has little effect on blood pressure in normotensive individuals (Maze 1988). It is important to emphasise that inhibition of central sympathetic output by alpha-2 adrenoceptor stimulation might be deleterious especially in patients in which sympathetic activity is essential for maintenance of circulatory function (e.g. chronic valvular disease). However, in contrast to the effects of beta receptor blocking agents and ganglion blockers clonidine neither alters catecholamine metabolism nor does it block ganglion transmission or adrenergic receptors. Thus, the protective reflexes triggered by a reduction in

blood pressure are still functional and vasoactive and inotropic drugs still remain effective despite prior administration of alpha-2 adrenoceptor agonists (Ruffolo 1985).

Intravenous administration of alpha-2 adrenoceptor agonists frequently lead to an initial increase in arterial blood pressure and systemic vascular resistance and a secondary decrease in heart rate resulting in a transient reduction of cardiac output (Kahn 1999). These effects are probably due to the activation of alpha-1 receptors and postjunctional vascular alpha-2 adrenoceptors. This first short period of increase in blood pressure is within minutes followed by a longer period characterised by a decrease in heart rate and arterial blood pressure due to a centrally mediated decrease in sympathetic tone (Feldberg 1954, Grunden 1969, Fugner 1971, Hossman 1980, Prichard 2000). The reduction in sympathetic tone results in a reduction of heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. The result of these effects is a net decrease in myocardial oxygen consumption which most probably explains the positive effects seen with alpha-2 adrenoceptor agonists in the treatment of angina pectoris (Zochowski 1984).

If clonidine is administered at doses above what can be considered as the normal dose range a biphasic dose-response relationship can be observed regarding the blood pressure response. Administration of lower doses of clonidine (< 10 mcg kg^{-1}), representing the normal therapeutic dose range, will result in a reduction of the systemic blood pressure whereas higher doses (> 10 mcg kg^{-1}) will cause an increase in blood pressure, most likely as a result of a direct effect on postjunctional alpha-1 and alpha-2 receptors at these higher dose levels (Figure 5).

Effects on systemic blood pressure after neuraxial administration

Neuraxial administration of alpha-2 adrenoceptor agonists produces a reduction of systemic blood pressure primarily by interactions at three different sites (Figure 5). Direct stimulation of alpha-2 adrenoceptors in the spinal cord will result in an inhibition of sympathetic preganglionic neurones (Guyenet 1981). Systemic absorption of neuroaxially administered alpha-2 adrenoceptor agonists will also give rise to interactions both with centres in the brainstem and possible exert direct effects on peripheral nerves. Activation of alpha-2 adrenoceptors and imidazoline-receptors in the brainstem will reduce central sympathetic outflow (De Vos 1994, Hamilton 1992) and stimulation of peripheral presynaptic sympathetic nerve endings will cause peripheral vasodilatation (Guyenet 1981). All the above effects are to a minor extent opposed by direct postsynaptic alpha-2 and alpha-1 stimulation of the vasculature causing vasoconstriction (Langer 1985). However, the net effect of lumbar

epidural alpha-2 adrenoceptor administration is a moderate reduction of blood pressure (maximum 20 %) in normotensive individuals (DeKock 1993). In contrast thoracic epidural administration of alpha-2 adrenoceptor agonists can produce more profound hypotension (DeKock 1991, Rauck 1993). The greater effect on blood pressure caused by thoracic epidural administration could possibly be explained by a more pronounced interference with the sympathetic neurones at the thoracic level of the spinal cord.
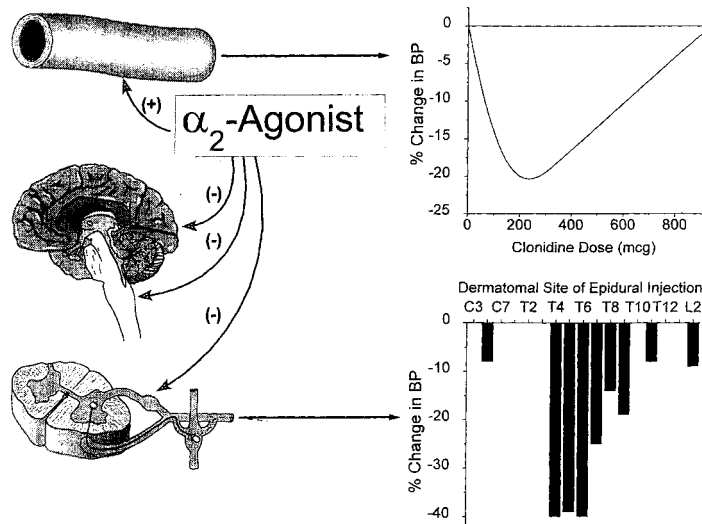

Figure 5. Sites of heamodynamic action of alpha-2 adrenoceptor agonists. (Eisenach 1996; with permission).

Effects on heart rate after systemic or neuraxial administration

Alpha-2 adrenoceptor agonists reduce heart rate by a presynaptically mediated inhibition of sympathetic tone caused by a reduction of noradrenaline release and by a direct vagotomimetic effect (De Jonge 1981). The gain of the baroreceptor system is increased resulting in lower heart rates for a given increase in blood pressure and the range of heart rate responses to changes in blood pressure is broaden (Badoer 1983).

Alpha-2 adrenoceptor agonist interaction at the level of T_{1-4} after epidural administration might effect the sympathetic innervation of the heart itself. The heart rate reduction after epidural clonidine is 5-20 % but clinically significant bradycardia, necessitating administration of atropine is rare (Eisenach 1996). The negative chronotropic and inotropic effects are counteracted by a reduction in afterload and in some patients cardiac output has been shown to increase (Eisenach 1996). The net effect on the myocardium of alpha-2 adrenoceptor activation is a reduction of oxygen consumption.

In summary, the haemodynamic effects of alpha-2 adrenoceptor agonists, both after neuraxial and intravenous administration, occur within approximately 30 min, reaches its maximum within 1-2 h, and lasts approximately 6-8 h after a single injection (Eisenach 1996). Delayed (> 2 hours) onset of haemodynamic effects after neuraxial or intravenous administration of alpha-2 adrenoceptor agonists has not been observed.

Alpha-2 adrenoceptor mediated analgesia sedation and anxiolysis

Antinociceptive effect.

Descending noradrenergic antinociceptive pathways originating in the brainstem are believed to be associated with analgesic effects by suppression of spinal nociceptive impulses (Fields 1978, Mayer 1974). Kita et al have recently demonstrated that the anaesthetic sparing effect of systemic clonidine is mediated by supraspinal, not spinal, alpha-2 adrenoceptors in cats (Kita 2000). A central mechanism for the analgesic action of alpha-2 adrenoceptor agonists has, however, been debated since direct administration of clonidine into the brainstem fails to produce analgesia (Coote 1988, Castro 1989). Others have suggested that the central analgesic action of systemic administered alpha-2 adrenoceptor agonists is mediated purely by its sedative actions by decreasing the unpleasant experience of pain (Priddle 1950).

Alpha-2a adrenoceptors have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord. Stimulation of these alpha-2 adrenoceptors inhibits the firing of nociceptive neurones stimulated by peripheral Aδ and C fibers (Howe 1983). Recent evidence suggests that the antinociception produced by alpha-2 adrenoceptor agonists may be due in part to acetylcholine release in the spinal cord (Bouaziz 1995, Klimscha 1997). Further evidence supporting the theory of a spinal action in alpha-2 adrenoceptor agonist mediated analgesia has been observed in humans. Firstly, a single lumbar epidural bolus injection of the alpha-2 adrenoceptor agonist clonidine produces analgesia in the lower, but not the upper, extremity (Eisenach 1993). Secondly, there appears to be a poor correlation between plasma concentrations of clonidine and analgesia, while there is a strong correlation between CSF concentrations of clonidine and analgesia (Mendez 1990). Thirdly, an intrathecal dose of clonidine of 150 mcg produces analgesia with a duration of 4-6 hours, while the analgesic effect of the same dose by epidural or i.m. routes produces no more analgesia than placebo (Bonnet 1990 A,B). Rescue pain medication (PCA) approaches zero when calculated CSF clonidine concentrations approach 130 ng ml^{-1} (Mendez 1990). In a further study Bernard et

al demonstrated that clonidine is twice as potent when administered epidurally as compared to intravenous administration (Bernard 1995).
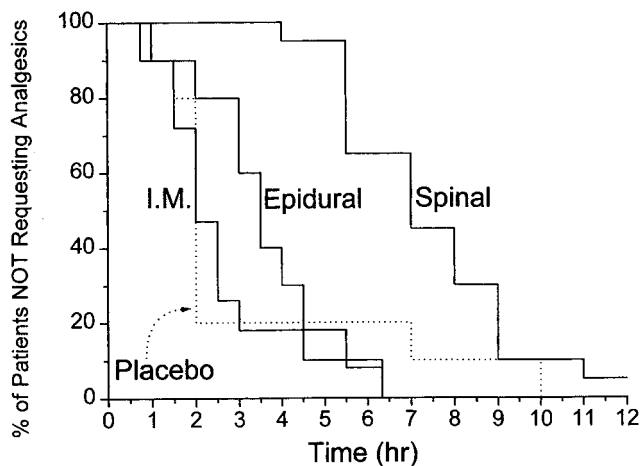

Figure 6. Effect of route of administration on the duration of analgesia of clonidine. (Eisenach 1996; with permission).

Sedation and anxiolysis.

The sedative and anxiolytic effects may be mediated by postsynaptic alpha-2a subtype adrenoceptors located in the locus coeruleus (Lidbrink 1974). Sedation produced by alpha-2 adrenoceptor agonists act synergistically with the sedative effect of benzodiazepines since the drugs are acting on different receptors (Dollery 1988). When monitored by EEG alpha-2 adrenoceptor agonists result in an attenuation of the physiological alpha fluctuations seen in untreated subjects and furthermore a maximal increase in slow wave activity (delta) is observed (Bischoff 1998). An increase in stage 1 and 2 sleep, and a reduction of rapid eye movement sleep has also be described (Hossman 1980). The anxiolytic effect is comparable to that of benzodiazepines (Ferrari 1989), however high doses have been reported to be anxiogenic, probably due to a direct alpha-1 effect (Soderpalm 1988). Alpha-2 adrenoceptor agonists have been proven to significantly improve the spatial working memory abilities of aged monkeys performing delayed-response tasks (Arnsten 1985).

2. Alpha-2 adrenoceptor agonists

Historical considerations and current medical use

Clonidine, the first adrenoceptor agonist with specificity for the alpha-2 adrenoceptor was first tested as a nasal decongestant but its associated effects on arterial blood pressure soon attracted attention and the drug was developed as an antihypertensive in the late 1960s

(Barnett 1968). Apart from their use in the treatment of hypertension (Mathias 1983), alpha-2 adrenoceptor agonists have been used to reduce afterload in patients with congestive heart failure (Giles 1981) and furthermore in the treatment of angina pectoris (Hermiller 1983).

Symptomatic bradycardia or orthostatic hypotension was rarely encountered during clonidine treatment but other side effects were noted. In the initial stages of treatment dry mouth and pronounced sedation were noticed in a proportion of patients. These side-effects were generally mild and the patients appeared to adapt quickly (Bock 1973). However, a serious withdrawal syndrome was seen after long term use and made it a less popular choice for the treatment of hypertension. The withdrawal syndrome, characterised by restlessness, insomnia, headache and nausea in association with hypertension and tachycardia results from rebound increase of sympathetic nervous activity (Hansson 1983). This rebound phenomena can be so severe as to cause secondary myocardial infarction and cerebral haemorrhage (Hansson 1983). The withdrawal syndrome has not been reported after short time use of clonidine (< 6 days) (Hokfelt 1970).

Alpha-2 adrenoceptor agonists are currently part of the routine treatment of opiate drug addiction and also for opioid weaning in ICU patients (Redmond 1982). In psychiatric practise, various withdrawal states i.e. benzodiazepine (Ashton 1987), alcohol (Cushman 1989) and nicotine (Glassman 1988) have successfully been treated with clonidine. Other psychiatric disorders such as panic attacks (Liebowitz 1984), hyperactivity in children (Hunt 1985), Korsakoff´s psychosis (Mair 1986) and Tourette´s syndrome (Cohen 1979) are also possible to treat with clonidine. Alpha-2 adrenoceptor agonists have been shown to be as effective as baclofen in reducing spasticity (Pellkofer 1989, Mathias 1989) and clonidine can also be used in the treatment of migraine (Wilkinson 1969, Brodgen 1975). Increased growth hormone secretion has been detected after clonidine treatment (Lal 1975) and this effect has been used to accelerate growth in children with growth delay (Pintor 1985).

Selective alpha-2 adrenoceptor agonists and antagonists

Clonidine is considered to be a mixed agonist that stimulates both alpha-1 adrenoceptors, alpha-2 adrenoceptors, and imidazolinreceptors (Van Zwieten 1997). The agonistic effect on alpha-2/alpha-1 adrenoceptors have a relationship of approximately 200/1 (Maze 1991). Due to the somewhat limited alpha-2 selectivity of clonidine more selective agents have been developed (Figure 7).
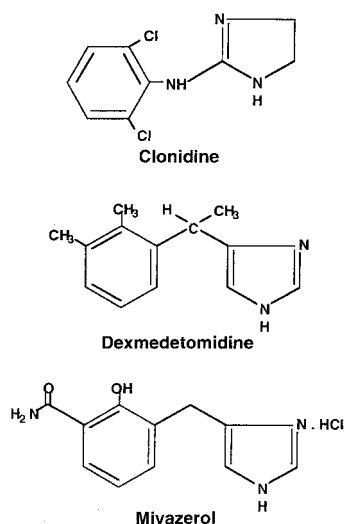
Figure 7. Chemical structure of clonidine, dexmedetomidine, and mivazerol. (Khan 1999; with permission).

Detomidine (Virtanen 1985, Clarke 1986) and medetomidine (Scheinin 1989) have become popular in veterinary anaesthesia and is often used in combination with ketamine (Jalanka 1989, Nevalainen 1989). Studies in man have been performed using both dexmedetomidine (Maze 2001) and mivazerol (Apitzsch 2000), but clonidine is still the only commercially available alpha-2 adrenoceptor agonist in Scandinavia.

Alpha-2 adrenoceptor antagonists that are able to reverse the effects of alpha-2 adrenoceptor agonists are now available (Table 3). This obviously is a benefit both in preclinical research and in the clinical use of potent alpha-2 adrenoceptor agonists. Yohimbine is the standard antagonist used for laboratory research (Pellow 1985) but cannot be used in higher doses in humans due to its side effects (Tam 2001). Tolazoline is often used in veterinary practice and can also be used in man (Schwartz 1998). More selective antagonists e.g. atipamezole are also available but further studies are required before they can be used in clinical practice (Schwartz 1998).

Non-selective alpha-2 adrenoceptor agonists	Selective alpha-2 adrenoceptor agonists
Noradrenaline	Dexmedetomidine
Adrenaline	Mivazerol
	Clonidine
	α-Methyldopa

Table 3. Selective and nonselective alpha-2 adrenoceptor antagonists. (Khan 1999; with permission).

Pharmacokinetics of clonidine in adults

Pharmacokinetics after systemic administration.

The pharmacokinetics of clonidine display a certain interindividual variability in adults but the pharmacodynamic response to the drug is however not affected by age (Van Zwieten 1997). Oral bioavailability is high (Klein 1990) ranging between 75 % (Hoffman 1996) and 95 % (Davies 1977, Frisk-Holmberg 1981, Arndts 1983), and due to its lipid solubility clonidine will readily penetrate extravascular sites as well as the central nervous system and the fetal circulation (Hoffman 1996, MacGregor 1985). Plasma binding is approximately 20-40 % (130 Hartikainen-Sorri 1987, Heckner 1979).

The pharmacokinetics of clonidine is best described by a two compartment model with a rapid distribution phase and a slow elimination phase (Hoffman 1996). The distribution half-time is approximately 10 minutes, and the elimination half time 8-13 h (Hoffman 1996, Davies 1977, Hulter 1979, Frisk-Holmberg 1978, Lowenthal 1988). The volume of distribution is within the 2.0-3.42 L kg^{-1} range, and the total body clearance varies from 3.05-4.85 mL kg^{-1} min^{-1} (Hoffman 1996, Davies 1977, Hulter 1979, Frisk-Holmberg 1978).

Clonidine is metabolised to approximately 50 % with the main metabolite, p-hydroxyclonidine which has been shown to be pharmacologically inactive (Dollery 1975). The elimination is mainly via the kidneys where approximately 40-50 % of the administered dose is eliminated unchanged (Hoffman 1996).

Clonidine can also be administered via a transdermal patch and therapeutic levels and steady state conditions are reached within 48 h and 72 h, respectively (Schwartz 1998). Transdermal clonidine application displays dose linearity (Arrndts 1979) and is associated with less adverse symptoms compared to oral administration (Wallenstein 1993).

New aspects on the pharmacokinetics of clonidine has emphasised that clonidine shows dose dependent pharmacokinetics with reduced plasma clearance after increasing intravenous doses (Frisk-Holmberg 1981). After multiple oral dosing reduced elimination rate constants and increased plasma clearance has been described, an observation that might be explained by reduced oral bioavailability (Davies 1977). The pharmacokinetics of the drug can be affected by entero-hepatic circulation, something that can affect the precision of the two compartment model (Frisk-Holmberg 1981).

Nasal administration in rodents shows a rapid (minutes) absorption similar to intravenous administration (Fujimura 1994). Oral and sublingual administration of clonidine has similar

pharmacokinetic and haemodynamic profiles (Babhair 1990). Pharmacokinetic data after rectal administration of clonidine in adults has so far not been reported in the literature.

Pharmacokinetics after neuraxial administration.

Tamsen and Gordh have demonstrated that epidurally administered clonidine in a porcine model readily penetrates the dura mater and displays minimal signs of toxicity (Cunningham 1994, Tamsen 1984 A). Later research, based on laboratory and extensive clinical experience, has been able to confirm the earlier findings of Thamsen and Gordh with regards to a low potential for neurotoxicity following spinal application of clonidine (Gordh 1986).

Fourteen percent of epidurally administered clonidine can be found in the cerebrospinal fluid, a value that is three times higher than that after intravenous administration (Hodgson 1999). After epidural clonidine administration peak concentrations in venous blood are reached within 10 min and in arterial blood after 30-40 min (Castro 1989, Eisenach 1993). The time to maximal CSF concentration after epidural administration is 30-60 min and the elimination half-life in CSF is 1.1-1.3 hours (Gordh 1988, Castro 1989, Glynn 1992, Eisenach 1993). In contrast to plasma levels, there is a strong correlation between clonidine concentration in CSF and analgesia after epidural clonidine administration supporting a spinal site of action of clonidine in producing analgesia (Gordh 1988, Castro 1989, Eisenach 1993). With prolonged infusions of epidural clonidine in cancer patients (14 days) there is no tendency to accumulation of clonidine in plasma (Glynn 1992).

Author	Dose	C_{max} (ng/ml)	T_{max} (min)	$T_{1/2}ab$ (min)	$T_{1/2}el$ (h)
Arterial plasma					
Eisenach[19]	700 μg	3.8 ± 0.6	12 ± 2	3.6 ± 0.4	15 ± 3.9
Gordh[94]	150 μg	1.1 ± 0.3	5 ± 1		14 ± 2.2
Venous plasma					
Eisenach[77]	1–900 μg	0.6 → 5.1	59 ± 45	11 ± 21	13 ± 11
Glynn[82]	150 μg	0.63	15–90		
Bonnet[23]	2 μg/kg	0.82 ± 0.22	68 ± 83		
Petit[169]	2 μg/kg	0.95 ± 0.10	40 ± 58		20 ± 6
Cerebrospinal fluid					
Eisenach[19]	700 μg	390 ± 240	31 ± 12	23 ± 9	1.3 ± 0.6
Glynn[82]	150 μg	228 ± 56	60 ± 7	31 ± 7	1.1 ± 0.1
Gordh[94]	3 μg/kg	203	30	1.1	

Table 4. Blood and cerbrospinal fluid pharmacokinetics of clonidine after neuraxial administration in adults. (Eisenach 1996; with permission).

Interactions with other drugs.

Synergy between the antinociceptive effects of intrathecal clonidine and systemic morphine has been proven in rats (Drasner 1988) as well as synergy in analgesic effect of co-administration of intrathecal clonidine and neostigmine (Pan 1998).

3. Alpha-2 adrenoceptor agonists and anaesthesia.

"Not poppy, nor mandragora, Nor all the drowsy syrups of the world, Shall ever medicine thee to that sweet sleep which thou owd´st yesterday." What Shakespeare refers to are extracts of Papaver somniferum (the opium poppy) and extracts of Mandragora officinarum (the mandrake) (Carter 1996).

The use of morphine, probably the most commonly used preanaesthetic analgesic of all times, unfortunately has many adverse effects such as respiratory depression, nausea, and allergic reactions. Tolerance to opioids has been demonstrated even after acute exposure both in animals (Fairbanks 1997) and in man (Vinik 1998). The development of tolerance and hyperalgesi seen with opioids might be explained by interactions with the NMDA-receptor since the NMDA-receptor antagonist ketamine prevents development of opioid induced tolerance and hyperalgesia (Trujillo 1991). Taking this into consideration ketamine might be a promising preanaesthetic. However due to the hallucinatory properties of ketamine its use as a preanaesthetic in paediatric anaesthesia has been restricted. Other analgesics such as NSAID´s are known to cause allergic reactions as well as bleeding problems (Splinter 1996) if combined with other anticoagulants. Such adverse effects are especially unwanted in patients receiving spinal or epidural anaesthesia (Armstrong 1999). Beta-adrenergic blocking agents may give rise to bronchoconstriction and bradycardia that might be difficult to antagonise. Benzodiazepines provide anxiolysis, sedation, and amnesia but are known to cause confusion and agitation in the elderly as well as in children (Schneider-Helmert 1985, Malviya 2000). A combination of benzodiazepines and opioids might be unfavourable since activation of GABA receptors is known to result in antagonism of opioid analgesia (Gear 1997). A comparison of the potential beneficial effects of clonidine compared to beneficial effects of different preanaesthetics are shown in table 5.

EFFECT	COMMONLY USED DRUGS	EFFECT OF CLONIDINE	
Anxiolysis	Benzodiazepines	Yes	(Scheinin 1989)
Sedation	"	Yes	(Dollery 1988)
Amnesia	,,	No	
Analgesia	Morphine, NSAID, paracetamol	Yes	(Xie 1986)
Reduced salivation	atropine, scopolamine, glycopyrrat	Yes	(Watkins 1980)
Vagolysis	,,	No	
Reduced gastric secretion	Cimetidin, ranitidin, omeprazol, sucralfat	Yes	(Cheng 1987)
Reduced acidity	,,	No	
Sympathicolytic effects	β- adrenoceptor antagonists	Yes	(Flacke 1987)
Reduced PONV	droperidol, ondansetron	Yes	(Kobayashi 1997)

Table 5. A comparison of commonly used preanaesthetics and clonidine. Halldin-Lindahl, Anestesi, Liber AB, modified with permission.

Alpha-2 adrenoceptor agonists use in veterinarian anaesthesia

Based on the sedative and antisialogogue properties of alpha-2 adrenoceptor agonists veterinarians in the beginning of the 1970s began to use these agents as premedication in horses undergoing surgical procedures (Clark 1969, Burns 1971). Xylacine (Rompun®), an early alpha-2 adrenoceptor agonist, was shown to provide sedation, analgesia and muscle relaxation in animals (Clark 1969, Burns 1971, Kerr 1972, McCashin 1975) but it was not until 1981 that these effects were found to result from stimulation of central alpha-2 adrenoceptors (Hsu 1981, Clough 1981).

Various alpha-2 adrenoceptor agonists, e.g. clonidine, medetomidine, dexmedetomidine and romifidine, are currently widely used in veterinarian anaesthesia. In this setting most alpha-2 adrenoceptor agonists appear to act in a similar manner when used in combination with other agents, with the greatest difference being related to their duration of action (England 1996). In order to minimise any undesirable side effects a combination of a low dose alpha-2 adrenoceptor agonists, an opioid, and a benzodiazepine derivative is recommended for

veterinary use (Paddleford 1999). The effects of an alpha-2 adrenoceptor agonist can effectively be antagonised by the antagonist atipamezole (Cullen 1996).

Initial use of alpha-2 adrenoceptor agonists in human adult anaesthesia

Due to the well-known rebound reaction following acute discontinuation of long-term antihypertensive treatment with clonidine, Kaukinen and co-workers decided to study the effects of continuing clondine administration throughout the perioperative period (Kaukinen 1979 A). They observed that continuous use of clonidine perioperatively appeared to "smoothen out" the entire perioperative haemodynamic profile (Kaukinen 1979 A). Later Kaukinen and Pyyko were the first to describe a reduction of the halothane-MAC when subcutaneous administration of clonidine was administrered in rabbits (Kaukinen 1979 B). Subsequently, Bloor and Flacke in 1982 demonstrated that clonidine reduced MAC for halothane in dogs by 50%, an effect that could be reversed by tolazoline (Bloor 1982). During the later part of the 1980s a number of studies reported clonidine to provide preoperative sedation (Ghignone 1986, Flacke 1987, Carabine 1991 A, B), increased perioperative haemodynamic stability (Ghignone 1987, Flacke 1987), and also a reduction of volatile anaesthetic requirements (Ghignone 1987, Flacke 1987, Ghignone 1988). An analgesic action of epidurally injected clonidine could also be demonstrated by Tamsen and Gordh in 1984 (Tamsen 1984 B).

These initial studies of the use of clonidine in adult anaesthesia have been followed by numerous additional studies within this field. A recent Medline search (search words: clonidine and anaesthesia) identified more than 719 publications. A brief summary of this literature is provided below.

Use of alpha-2 adrenoceptor agonists in adult anaesthesia

When discussing the use of clonidine in general anaesthesia it is important to emphasise that clonidine is only capable of decreasing blood pressure that is dependent on sympathetic tone and, thus, has little effect on blood pressure in normotensive individuals (Maze 1988). Furthermore, the baroreceptor reflex is maintained after a clonidine challenge, although the threshold is reset at a lower level (Badoer 1983). Important protective physiologic reflexes are left intact since clonidine does not interfere with catecholamine metabolism or ganglion transmission and a full range of clinically useful vasoactive drugs still remain effective in the clinical setting (Maze 1988). This is in sharp contrast to the situation of perioperative administration of beta-adrenergic blocking drugs.

Effects on haemodynamic stability, stress response, and myocardial oxygen consumption

In a large study of patients undergoing major abdominal surgery De Kock and colleagues reported less adverse haemodynamic events after an intravenous bolus injection of clonidine at induction of anaesthesia (4 mcg kg^{-1}) followed by a subsequent continuos infusion of 2 mcg kg^{-1} h^{-1}, compared to patients treated with placebo (De Kock 1995). Pre-treatment with clonidine has also been shown to be more effective than a combination of lignocaine and fentanyl at blocking the cardiovascular response associated with laryngoscopy (Ghignone 1987). In patients undergoing cardiopulmonary bypass Flacke et al observed that clonidine not only reduce narcotic requirement by 40%, but also resulted in significantly lowered heart rate and blood pressure values both before and after induction of anaesthesia as well as following endotracheal intubation and after skin incision (Flacke 1987). Furthermore plasma catecholamine levels remained lower at all studied time points, and a higher cardiac output and lower systemic vascular resistance was found in the post-cardiopulmonary bypass phase (Flacke 1987). The attenuation of stress related sympathetic outflow by clonidine has been reported to result in better perioperative haemodynamic stability when compared to fentanyl, sufentanil, or lignocaine (Ghignone 1986, Ghignone 1987, Flacke 1987).

Based on such observations as described above it has been concluded that a "preoperative pharmacological sympathectomy" with clonidine in oral doses $\leq$ 5 mcg kg^{-1} appears to be a safe and useful stabiliser of both heart rate and blood pressure as well as myocardial performance (Roizen 1988).

The clonidine-induced reduction of heart rate, blood pressure, systemic metabolism, myocardial contractility and systemic vascular resistance provides a net reduction in myocardial oxygen consumption especially beneficial in patients with coronary disease (Zochowski 1984).

As with all medical treatments the use of clonidine can be associated with unwanted side effects. Although the general spectrum of side effects is rather benign more clinically important adverse effects such as hypotension and bradycardia have an average incidence of 14% in adult patients (Ghignone 1986, Stone 1988, Quintin 1990). However, due to the preserved responsiveness of the cardiovascular system as mentioned above these haemodynamic side effects are usually mild and can be effectively treated with anticholinergics, volume substitution, and/or inotropes.

Although strict contraindications to the use of clonidine are few clonidine should be avoided in patients with prolonged P-R intervals and spontaneous bradycardia (Weerasuriya 1984). The well-known withdrawal syndrome with restlessness, tachycardia and pronounced rebound

hypertension (Hansson 1983) occurring following acute discontinuation of chronic antihypertensive treatment with clonidine has not been reported after short time use of clonidine (< 6 days) (Hokfelt 1970).

Anaesthetic requirements

The requirement for both volatile agents and opioids has been reported to be reduced by approximately 40-50 % after pre-treatment with clonidine in adult humans (Bloor 1982, Ghignone 1987, Maze 1987). In MAC studies a ceiling effect appear to exist since a tenfold increase in clonidine dose does not decrease anaesthetic requirements further (Bloor 1982, Maze 1987). If anaesthetic depth is evaluated by EEG criteria, an oral dose of 5 mcg kg^{-1} of clonidine 90 min prior to surgery has been found capable of reducing fentanyl requirements by 45 %-74 % (Ghignone 1986, Maze 1988). This opioid sparing effect might, however, not only be a true pharmacological effect of clonidine *per se* since clonidine has been reported to increase plasma alfentanil concentrations by 60 % (Segal 1991).

The reduced need for both volatile agents as well as opioids is generally seen as a beneficial effect of alpha-2 adrenoceptor agonists. Aanta and Kanto have highlighted the danger that the reduced anaesthetic requirements and the modification of the haemodynamic response to a surgical stimulus caused by the administration of alpha-2 adrenoceptor agonists, may lead to an increased incidence of awareness (Aantaa 1992). However, this concern has not hitherto been substantiated by any published studies or case reports.

Sedation and anxiolysis

The observation of the sedative properties of clonidine was made in the first clinical trial of clonidine as a nasal decongestant, where a volunteer slept for 24 hours following the intranasal administration of 1-2 mg of clonidine (Walland 1977). Clonidine has later been shown to produces sedation in a dose-related fashion (Carabine 1991 A,B). Initial signs of sedation are seen at a plasma level ranging between 0.2-2.0 ng mL^{-1} in adult volunteers (Davies 1977). Alpha-2 adrenoceptor agonists also have a synergistic sedative effect when co-administered with benzodiazepines (Salonen 1992). It has been questioned whether the sedative actions may contribute to the analgesic effects of clonidine by simply decreasing the subjective unpleasantness of pain (Priddle 1950).

Despite the sedative properties of clonidine most studies report faster recovery from anaesthesia and less postoperative sedation in adult patients when compared to standard

techniques (Kumar 1994). This observation is most likely an effect of the reduced needs for both volatile agents as well as opioids as described above.

It is also important to consider the difference in the quality of sedation produced by clonidine compared to for example bensodiazepines. Clonidine lacks the psychotropic quality of bensodiazepines and will cause a state of sedation more similar to normal tiredness-sleepiness where the patient can easily be awoken to perform tests (Hall 2001). A further difference compared to bensodiazepines is that clonidine is frequently described as enhancing memory, especially in early stages of Alzheimer's disease (Riekkinen 1999), whereas bensodiazepines impair memory function and even produces amnesia (Echeverry 2001, Huron 2001).

Apart from the sedative properties of clonidine this drug also produces a moderate anxiolytic effect which is independent of sedation (Kruse 1981). The anxiolytic effect of 5 mcg kg^{-1} of oral clonidine has been reported to be equal to that of 100 mcg kg^{-1} of oral midazolam (Frank 2000).

Analgesic effects

In 1974 Paalzow and co-workers were the first to report clonidine to be a potent analgesic in animals (Paalzow 1974). The anatomical site associated with this analgesic action of clonidine as well as the pharmacological mechanisms for this analgesic effect is still debated.

Descending noradrenergic antinociceptive pathways originating in the brainstem have been shown to contribute to pain control by suppression of spinal nociceptive impulses by interaction with postjunctional alpha-2 adrenoceptors in the dorsal horn (Mayer 1974, Fields 1978) and is generally believed to be one of the main mechanisms of descending endogenous pain modulation. Thus, interaction with alpha-2 adrenoceptors in the dorsal horn normally responsible for endogenous pain modulation might be one possible mechanism for the antinociceptive action of clonidine (see below). However, since direct administration of clonidine into the brainstem does not produce analgesia (Coote 1988, Castro 1989) a more central mechanism for the analgesic action of alpha-2 adrenoceptor agonists has been hypothesised. Finally, as has been mentioned above, the central analgesic action of systemic administered alpha-2 adrenoceptor agonists has by some critics been solely attributed to the sedative actions of alpha-2 adrenoceptor agonists, thereby merely decreasing the unpleasantness of the pain experience (Priddle 1950).

Although other mechanisms are discussed the most widely accepted theory regarding the antinociceptive action of clonidine is believed to be spinal modulation (Eisenach 1996).

Alpha-2a adrenoceptors have been identified in the substantia gelatinosa of the dorsal horn of the spinal cord and stimulation of these alpha-2 adrenoceptors inhibits the firing of nociceptive neurones stimulated by peripheral Aδ and C fibers (Howe 1983). Recent evidence suggests that the antinociception produced by alpha-2 adrenoceptor agonists may be due in part to acetylcholine release in the spinal cord (Bouaziz 1995, Klimscha 1997) (see further discussion below; Clonidine in regional anaesthesia). Systemically administered clonidine have a documented analgesic effect (Hall 2001), but since the spinal cord is suggested to be the major site of analgesic action of alpha-2 adrenoceptor agonists (Eisenach 1993), the epidural and intrathecal routes have been considered preferable to the intravenous route. This is, however, questioned by data showing a similar effect of orally administered clonidine when compared to intrathecally applied clonidine in the context of spinal anaesthesia (Kita 2000).

Apart from a beneficial effect in acute pain alpha-2 adrenoceptor agonists have also been reported to be useful in the treatment of chronic pain syndromes in both animal and human studies (Puke 1993, Yaksh 1995, Leiphart 1995). The epidural route has proved the most effective way of administrating clonidine in neurophatic pain (Caroll 1993), although both intravenous and transdermal routes have been used (Byas-Smith 1995). A combination of epidural clonidine and local anaesthetics is particularly effective in patients suffering from neurophatic pain syndromes (Glynn 1995). Epidural clonidine has also been reported to be effective in treating cancer pain in patients tolerant to opioids (Eisenach 1989, Eisenach 1995 A) and topical clonidine has been found beneficial in the treatment of sympathetic mediated pain states (Davies 1991).

Other clinical effects of clonidine relevant to general anaesthesia

As stated earlier clonidine has little or no effect on respiration in normal doses (Ooi 1991) and the addition of opioids does not lead to any further depression (Baily 1991, Jarvis 1992). Flacke et al (Flacke 1987) could demonstrate a reduction in the time to extubation by 30% presumably resulting from a reduced intraoperative requirement of opioids (Flacke 1987).

Clonidine also exhibits positive effects on renal function in relationship to surgical stress with a reduction of both ADH (Humphreys 1975, Kimura 1981) and renin release (Smyth 1987). Furthermore, GFR is increased and the net effect of clonidine administration is increased diuresis and natriuresis in all studied species (Humphreys 1975, Lieper 1990). The potential of clonidine in this respect is illustrated by its effects in association with coronary artery bypass graft surgery. In this situation the normal postoperative deterioration in renal

function, as evidenced by an increase in serum creatinine levels or better preservation of creatinine clearance, is more or less prevented in patients pre-treated with clonidine (Lieper 1990, Myles 1999).

Clonidine has also been reported to reduce postoperative shivering both after general anaesthesia (Buggy 1997) and spinal anaesthesia (Mao 1998) and the incidence of postoperative nausea and vomiting (PONV) has been shown to be reduced after both systemic and epidurally administered clonidine (Kobayashi 1997, Oddby_Muhrbeck 2002).

Reduced salivation and reduced gastric secretion is seen after clonidine administration (Watkins 1980, Cheng 1987). However, no net change in gastric pH was observed following alpha-2 adrenoceptor administration (Orko 1987).

Clonidine in regional anaesthesia

A large body of literature supports an analgesic action of clonidine when used either alone or as an adjunct to other drug, e.g. local anaesthetics or opioids. Clonidine has been reported to enhance the sensory and motor blockade of local anaesthetics following both central and peripheral nerve blockade. This action has been attributed to a conduction block of C- and Aδ-fibers (Butterworth 1993). In animals intrathecal alpha-2 adrenoceptor agonists cause analgesia, in part, by spinal cholinergic activation in the dorsal horn of the medulla (Gordh 1989, Detweiler 1993, Klimscha 1997). Increased concentrations of acetylcholine in lumbar human CSF has been detected after epidural clonidine (Eisenach 1995 B), and epidural clonidine analgesia is enhanced by intrathecal injection of neostigmine (Hood 1995). When administered intrathecally together with fentanyl, clonidine produces a synergistic analgesic effect making a reduction of each component by 60 % possible (Eisenach 1994).

Opioids and neostigmine enhance intraspinal alpha-2 adrenoceptor agonist analgesia, while alpha-2 adrenoceptor agonists enhance both peripheral and central blockade accomplished by the administration of local anaesthetics. A combination of all these three separate classes of analgesic agents might enable a dramatic reduction in the dose of each compound, potentially reducing adverse reactions (Eisenach 1996).

Epidural administration

As is stated above clonidine in combination with local anaesthetics enhance both the motor and sensory quality of an epidural blockade (Eisenach 1996). Epidural clonidine prolongs postoperative pain relief alone (DeKock 1993) or in combination with sufentanil and/or bupivacaine (Hering 1996). In patients undergoing hip surgery a three-fold increase in the

duration of an epidural block is seen when 150 mcg of clonidine is added to 10 mL 0.5 % bupivacaine (Klimscha 1995). Epidural clonidine administered together with bupivacaine has also been shown to be effective for obstetric use and a single dose of 75 mcg of clonidine appears appropriate in this setting (Cigarini 1992, LePolain 1993, Brichant 1994).

The analgesic effect of clonidine within the dose range 150-600 mcg is accomplished with a similar effect on blood pressure as epidural bupivacaine (Klimscha 1995) or lignocaine (Nishikawa 1990) alone, and does not interfere with the responsiveness to ephedrine (Eisenach 1996) (Table 6).

Dose (μg)	N	Analgesia Duration (h)	Maximum Decrease in Blood Pressure (%)
160 (145–210)	110	2.7	−18
375 (300–450)	40	6.0	−21
597 (500–800)	31	5.1	−23

Data are means weighted by number of patients receiving each individual dose within the range. Data from 12 reports.[22,23,29,93–98,100,102,106]

Table 6. Duration of analgesic and blood pressure effect of epidural clonidine alone after surgery. (Eisenach 1996; with permission).

The relative haemodynamic safety of clonidine is further illustrated by the 181 patients reported by Eisenach and co-workers (Eisenach 1996). Although an epidural bolus dose of clonidine made volume loading necessary in several patients to treat a reduction of blood pressure, no patients required treatment with vasopressors and only 1 % needed treatment with atropine due to a reduced heart rate.

Intrathecal administration

Similar to epidural administration intrathecal clonidine (75-225 mcg) prolongs both the sensory and motor blockade of intrathecal bupivacaine (Racle 1987, Bonnet 1989, Bonnet 1990 B, Fogarty 1993). Since clonidine is a lipophilic drug (similar to fentanyl and sufentanil), one would expect a better effect profile after intrathecal application as compared to epidural administration. This assumption is supported by animal data from Eisenach et al who suggest a more than 6-fold potence ratio of intrathecal:epidural administration of clonidine for acute pain (Eisenach 2000). However, regarding mechanical hypersensitivity only a less than 2-fold potence ratio could be observed (Eisenach 2000). The reason for this discrepancy between acute pain and mechanical hypersensitivity still remains unclear.

The maximal decrease in blood pressure following an intrathecal block is only slightly increased when clonidine 75-225 mcg is added to 15 mg of bupivacaine since an almost total sympatholysis is caused by the local anaesthetic alone (Racle 1987, Bonnet 1989, Bonnet 1990 B, Fogarty 1993). The blood pressure reduction is less pronounced after 300-450 mcg than after only 150 mcg (Eisenach 1996), a finding that is consistent with the theory of peripheral alpha-1 adrenoceptor simulation after higher doses of clonidine resulting in peripheral vasoconstriction and a net increase in blood pressure (Langer 1985).

Peripheral administration

Clonidine in combination with local anaesthetics prolongs the duration of peripheral nerve blocks compared to local anaesthetics alone (Murphy 2000, Casati 2000, El Saied 2000). This effect has so far mainly been described when clonidine has been administered in association with brachial plexus blocks (Murphy 2000, El Saied 2000). Since systemically or intramuscularly administered clonidine does not produce this effect a local neural effect has been speculated (Singelyn 1992). However, when given as the sole analgesic for peripheral nerve blocks clonidine has not been found effective (Sia 1999). Despite the demonstration of the presence of alpha-2 adrenoceptors in peripheral nerve membranes in dogs (Daniel 1995) the mechanism for the adjunct effect of clonidine in the context of peripheral nerve blockades currently remain in part unsolved. Clonidine has also been used in combination with local anaesthetics in intravenous regional anaesthesia (Reuben 1999, Lurie 2000) and has in this setting been suggested to both improve postoperative analgesia (Reuben 1999) and to delay the onset of tourniquet pain (Lurie 2000).

Use of clonidine in the treatment of chronic pain

Epidural clonidine is effective in treating opioid resistant cancer pain, especially if the pain is believed to have a neuropathic pain component (Strube 1984, Eisenach 1995 A). In patients with non-cancer pain epidural clonidine has been reported to be effective in low back pain syndromes (Glynn 1993), deafferation pain after spinal injury (Glynn 1986, Glynn 1992), phantom limb pain (Jahangiri 1994), and reflex sympathetic dystrophy pain (Rauk 1993).

Sedation and respiratory effects after neuraxial administration

Regardless of route of administration clonidine will produce sedation in a dose-dependent fashion within the dose range of 50-900 mcg in adults (Eisenach 1996). The onset of sedation is rapid and usually occurs in less than 20 minutes (Eisenach 1996). The sedation after

epidural administration of clonidine is believed to be caused by systemic absorption from the epidural space with secondary redistribution to higher centres (Eisenach 1996). In contrast to epidurally administered morphine where delayed onset of sedation has been reported, no such delayed onset of sedation has been observed after neuraxial administration of clonidine (Eisenach 1996). After epidural bolus administration of 150 mcg or 400 mcg of clonidine sedation usually will last for 1-2 h or 2-4 h, respectively (Eisenach 1996). If used as a continuous epidural infusion after surgery, clonidine 40 mcg h^{-1} was found to produce similar sedation as compared to an epidural placebo combined with PCA morphine (Mendez 1990, Huntoon 1992).

Studies of both epidural clonidine in combination with morphine (Massone 1998), and a combination of low dose epidural clonidine, sufentanil, and bupivacaine has been unable to detect any clinically relevant degree of respiratory depression (Hering 1996). Two human volunteer studies have also failed to demonstrate any respiratory depression after systemic administration of clonidine in combination with opioids (Ooi 1991, Baily 1991). Thus, it has been concluded that, when administered in therapeutic doses, alpha-2 adrenergic agonists alone do not induce respiratory depression (Marruecos 1988), nor do they potentiate respiratory depression from opioids (Anderson 1981, Ooi 1991). In spite of this, a greater incidence of respiratory depression after epidural clonidine has been reported in certain studies (Narchi 1992, Penon 1991). However, the validity of these findings may be questioned given the absence of a control groups in these studies. According to Eisenach such respiratory depression could potentially occur if the pain relief accomplished by clonidine will unmask the respiratory depression from other drugs administered concurrently (Eisenach 1996).

4. Clonidine in paediatric anaesthesia

Prior to the use of clonidine in paediatric anaesthesia this drug had already been used in children to treat a variety of medical conditions. The first report of clonidine treatment in children dates back to 1973 when clonidine was used to treat migraine headache (Wall 1973). Following the finding that oral clonidine could stimulate growth hormone release (Lal 1975) a clonidine challenge test was introduced as a diagnostic tool in growth hormone deficiency syndromes (Gil-Ad 1979). Beneficial effects of clonidine medication could also be demonstrated in children with Tourette syndrome (Cohen 1979) as well as in children with

attention-deficit hyperactivity disorder (ADHD) (Rostain 1991). Clonidine has furthermore been used in the treatment of paediatric hypertension (Binde 1979).

Despite the promising effects of clonidine achieved in adult anaesthesia it was not until the early 1990s that this drug received attention in the context of paediatric anaesthesia. Simultaneously with the start of the present thesis project the first report on the clinical use of clonidine in paediatric anaesthesia was published by the Japanese Kobe group. Thus, in 1993 Mikawa and co-workers published their first report on the use of oral premedication with clonidine in children (Mikawa 1993). A brief summary of the currently known effects of clonidine in paediatric anaesthesia is outlined below.

Premedication in children

Whether premedication is necessary in children or not is currently debated. Hatava and Olsson have demonstrated that preoperative psychological preparation and parental presence is obviously beneficial (Hatava 2000). On the other hand sedative premedication with midazolam is more effective than either parental presence or no intervention at all in managing child-parent anxiety during the preoperative period (Kain 1998). The level of anxiety is of course individual, with children who have previous negative experiences from operations or painful procedures showing more anxiety (Breitkopf 1986). Premedication is not only advantageous in conjunction with surgery but can also be desirable before other painful and/or stressful invasive procedures.

Preoperative sedation

In their initial study Mikawa et al reported that oral clonidine 4 mcg kg^{-1} administered 105 minutes prior to anaesthetic induction provided improved sedation, better quality of separation from parents, and a higher acceptance rate of mask application compared to clonidine 2 mcg kg^{-1} or diazepam 0.4 mg kg^{-1} (Mikawa 1993). This beneficial effect of clonidine premedication was later supported by Ramesh and colleagues who showed that oral clonidine 3 mcg kg^{-1} produced comparable sedation to diazepam 0.2 mg kg^{-1}, but was also found able to attenuate the haemodynamic response to endotracheal intubation without any prolongation of the recovery time from anaesthesia compared to diazepam (Ramesh 1997). In neither of these studies were adverse effects such as bradycardia, hypotension or respiratory depression noted.

The sedative and anxiolytic effect of oral clonidine (4 mcg kg-1) was later compared to that of oral midazolam (0.5 mg kg^{-1}) by Lavrich and co-workers (Lavrich 1996). They reported that both drugs produce similar degrees of sedation and anxiolysis in paediatric surgical patients.

Although midazolam currently at many institutions represent the gold standard for preoperative sedation, it should be taken in to account that the use of midazolam in this context has been found to be associated with an increased incidence of adverse postoperative behaviour, e.g. nightmares, night terrors, food rejection, anxiety, and negativism (McGraw 1998).

Effects on the stress response secondary to endotracheal intubation and surgery

In line with previous adult findings several paediatric studies have shown that oral administration of clonidine is capable of blunting both the catecholamine release and the haemodynamic response secondary to endotracheal intubation in otherwise healthy children 7-17 yrs (Mikawa 1993, Ramesh 1997, Mikawa 1995 A). In a recent study by Nishina et al oral clonidine premedication was found to attenuate the hyperglycaemic response to surgical stress (Nishina 1998). These authors suggested that a 2 % glucose infusion would to be optimal in order to maintain blood glucose concentrations within the physiologic range when using this approach.

Anaesthetic sparing effect

Oral clonidine premedication with 2-4 mcg kg^{-1} in children aged 7-12 yrs successfully decrease the dose of intravenous barbiturate required for induction of anaesthesia (Nishina 1994). The effect of clonidine on propofol requirements for anaesthetic induction has yet not been evaluated. Compared to placebo, oral clonidine treatment with 4 mcg kg^{-1} in children undergoing minor surgery has been demonstrated to both reduce the halothane requirements for maintenance of anaesthesia (Nishina 1996) as well as the MAC_{TI} of sevoflurane for endotracheal intubation (Nishina 1997).

Supplement to regional anaesthesia and postoperative analgesia

The administration of clonidine (1-5 mcg kg^{-1}) as an adjunct to local anaesthetics have repeatedly been found to prolong and improve postoperative pain relief following caudal blockade in children (Jamali 1994, Lee 1994, Cook 1995, Ivani 1996, Motsch 1997, Klimscha 1998, Ivani 2000). The first two published studies in this field published by Jamali and Lee &

Rubin in 1994 could demonstrate that clonidine was able to almost double the duration of the caudal block compared to bupivacaine alone. This was also accomplished without the occurrence of any significant side effects. The addition of an epidural clonidine infusion (0.08-0.12 mcg kg^{-1} h^{-1}) to a continuous epidural infusion of ropivacaine has lately been found to improve the quality of postoperative pain relief in children (De Negri 2001 A).

Oral clonidine has been shown to be less potent than epidural clonidine regarding the enhancement of epidural blockade caused by local anaesthetics than in adults (Mendez 1990). However, the administration of oral clonidine 5 mcg kg^{-1} has been reported to cause an increased duration of bupivacaine induced caudal anaesthesia in children (Goodarzi 1996).

Caudal administration

Author	Age (yrs)	Dose (mcg kg^{-1})
Jamali 1994	1-7	1
Ivani 1996	1-10	2
Lee 1994	1-10	2
Motsch 1997	4-8	5
Klimscha 1998	0.5-6	1-2
Cook 1995	1-10	2
Ivani 2000	1-10	2
DeNegri 2001	1-5	2

Epidural administration

Author	Age (yrs)	Dose (mcg kg^{-1})
Boos 1996 (n = 3)	1-19	2
Portas 1998 (n = 7)	1-15	5-10

Postoperative epidural infusion

Author	Age (yrs)	Dose (mcg kg^{-1} h^{-1})
De Negri 2001	1-4	0.04-0.12

Local infiltration

Author	Age (yrs)	Dose (mcg kg^{-1})
Giannoni 2001	3-15	1

Table 7. Beneficial effects of adjunct use of clonidine in paediatric anaesthesia. (Nishina 1999; with permission).

Effects on gastric pH and postoperative emesis

In adults clonidine reduce the volume of gastric content (Kaess 1971), while gastric pH is left unaffected (Orko 1987). This issue has so far only been investigated in one paediatric study where oral clonidine (4 mcg kg^{-1}) did not affected gastric fluid volume or pH compared to placebo (Nishina 1995). Regarding postoperative nausea and vomiting both oral and caudal clonidine have been reported to reduce the incidence of postoperative vomiting in children (Mikawa 1995 B, Motsch 1997).

Adverse effects

In general clonidine has not been shown to cause any interference with ventilation and does not potentiate opioid induced respiratory depression (Baily 1991). However, respiratory depression has been reported following massive clonidine overdose (Olson 1983, Anderson 1981). Two case reports has also been published suggesting that clonidine administration potentially contributed to the development of postoperative apnoea in preterm infants treated with a caudal technique including clondine administration (Breschan 1999, Bouchut 2001). However, no conclusive argument to attribute this adverse effect to clonidine could be given in these reports. Further support for the benign effect of clonidine on ventilation is given in a recent case report where a 1000-fold unintentional overdose of clonidine was found not to cause any signs of respiratory depression (Romano 2001).

Although clonidine can induce hypotension and bradycardia serious adverse effects such as pronounced hypotension and bradycardia have not been reported in children when using doses of clonidine less than 10 mcg kg^{-1} (Nishina 1999).

Clonidine poisoning

The incidence of clonidine poisoning in children is low compared to other drugs. The adverse reactions following overdose include pallor, bradycardia, hypotension, miosis, unconsciousness, hypotonia, and hypothermia (Fiser 1990, Wiley 1990, Anderson 1981, Artman 1983, Olsson 1983). Peripherally mediated alpha-2 adrenergic effects such as hypertension and vasoconstriction are often reported in adults after higher doses of clonidine (> 10 mcg kg^{-1}) but are less common in children. A very important argument for the inherent safety of clonidine is the fact that there are no reports of death that can obviously be related to overdose of clonidine. A few cases of sudden unexplained deaths in children have been reported after clonidine intoxication in combination with other drugs, but in these cases the relationship to clonidine was thought to be negligible (Maloney 1995). In one case of

pharmacy compounding error in which micrograms erroneously were substituted for milligrams a 5-year old child received a 1000 fold overdose (50 mg) of clonidine (Romano 2001). One of the initial symptoms was reported was hyperventilation, a finding that previously has not been described. The child was discharged after 42 h without any sequelae.

The pharmacological treatment of bradycardia and hypotension caused by clonidine poisoning include administration of atropine, volume expansion and dopamine infusion (Hoffman 1996). A positive response to naloxone treatment has been reported in some cases where clonidine overdose has been associated with respiratory depression (Fiser 1990).

THE THESIS

Rationale for the thesis

Based on the review of the current literature presented above clonidine and other alpha-2 adrenoceptor agonists are capable of producing a number of beneficial effects in the setting of both general and regional anaesthesia. Despite recent contributions regarding the clinical use of clonidine in children further studies delineating the specific pharmacokinetic and haemodynamic characteristics of this compound in the context of paediatric anaesthesia is needed in order to provide safe and effective use of this drug in children. Furthermore, randomised controlled trials comparing the clinical use of clonidine as a premedicant drug to the current gold standard represented by midazolam are warranted. Against this background the following aims for the thesis were decided:

AIMS OF THE THESIS:

1. to describe the pharmacokinetics of clonidine after intravenous, rectal, and epidural administration in children (Studies I, II, and IV).

2. to delineate the haemodynamic profile of intravenous clonidine in children during unstimulated isoflurane anaesthesia (Study I) and,

3. to determine if a haemodynamic dose-response relationship is present for intravenous clonidine within the dose range 0.625-2.5 mcg kg^{-1} during paediatric anaesthesia (Study III).

4. to evaluate the postoperative analgesic and sedative effects of clonidine after epidural co-administration together with bupivacaine (Study IV).

5. to investigate the magnitude of the stress-response caused by endotracheal intubation in children, with special emphasis on the Neuropeptide Y response (Study V) and,

6. to determine if clonidine is capable of attenuating the stress-response associated with endotracheal intubation compared to midazolam (Study V).

7. to determine if a postoperative epidural co-infusion of clonidine together with ropivacaine influences blood pressure variability (Study VI).

8. to compare clonidine *vs.* midazolam regarding postoperative analgesia, sedation, delirium, shivering and postoperative vomiting during the early postoperative phase after adeno-tonsillectomy in children (Study VII).

MATERIALS AND METHODS

The studies were performed in accordance with the Declaration of Helsinki. All studies were approved by the Local Ethics Committee and parental consent was obtained in all cases.

Patient populations and demographics:

A total of 238 individual paediatric patients were included in the studies as specified below:

Paper I: Twelve paediatric ASA I patients (age: 31 months (SD 11), weight: 14.4 kg (SD 3.1) scheduled for inguinal hernia repair on an out-patient basis.

Paper II: Ten paediatric ASA I patients (age range: 14-48 months, weight range: 10-20 kg) scheduled for inguinal hernia repair on an out-patient basis.

Paper III: 24 paediatric ASA I (age range: 13-78 months, weight range: 10-20 kg) scheduled for minor surgery (e.g. inguinal hernia repair and orchidopexy).

Paper IV: 8 paediatric ASA I patients (age range: 1-9 yrs, weight range: 9-41 kg) scheduled for urethral surgery.

Paper V: 20 paediatric ASA I patients (age range: 16-98 months, weight range: 10-20 kg) scheduled for minor surgery (inguinal hernia repair, orchidopexy and adenoidectomy).

Paper VI: 60 paediatric ASA I –II patients (age range: 1-4 years, weight range: 6-20 kg) undergoing hypospadias repair.

Paper VII: 104 paediatric ASA I patients (age range: 1-11 years, weight range: 10-57 kg) scheduled for adeno-tonsillectomy.

A majority of the studied patients were boys (boys: n = 170, girls: n = 68). The dominance of boys is mainly explained by the surgical diagnoses of the investigated patients (hypospadia, retentio testis, and inguinal hernia repair), which exclusively or mainly occur in males. No significant differences with regard to demographic data were detected between the study groups in the comparative studies Studies V and VII.

Premedication

Atropine was included in the premedication in all studies except in study VI. Apart from clonidine the following additional premedication agents were used in the studies:

1. Rectal midazolam 300 mcg kg^{-1} (Study I, III, V, VII).
2. Intravenous morphine 75 mcg kg^{-1} (Study II).

3. Oral diazepam 400 mcg kg^{-1} (Study VI).
4. Oral flunitrazepam 30 mcg kg^{-1} (Study IV).

Anaesthetic methods

In studies I, II, III, and VI airway management was performed with a regular face mask whereas in studies IV, V, and VII airway management was handled with endotracheal intubation. In studies I-VII an inhalation agent (isoflurane or sevoflurane) combined with nitrous oxide and oxygen was used for anaesthetic maintenance. In study IV the maintenance anaesthetic in some patients consisted of a continuous propofol infusion.

Dosage of clonidine and route of administration

The following dosages of clonidine were used:

Bolus doses: 0.625, 1.25, 2.5, and 5.0 mcg kg^{-1}.

Continuous infusion: 0.04, 0.08, and 0.12 mcg kg^{-1} h^{-1}.

Routes of administration: epidural, intravenous, and rectal.

Clonidine assay

The blood samples were immediately anticoagulated with heparin and centrifuged and the plasma was frozen (-20° C) until analysis. Clonidine analysis was performed by radioimmuno-assay (Boehringer Ingelheim, Frankfurt, Germany). The detection limit of the assay was 0.1 ng mL^{-1}. At reference levels 0.20, 0.50, and 1.00 ng mL^{-1} the deviation of the found values were 0, -2, and −9 % of the reference values, respectively. Inter- and intra-assay coefficients of variation were $\pm$ 5-8 % and $\pm$ 4-5 %, respectively.

Determinations of noradrenaline and Neuropeptide Y

In paper V plasma was frozen at − 70° C immediately after centrifugation and stored until final analysis. For NA determinations the samples were analysed using a high performance liquid chromatography system (Stenfors 1995). NPY was analysed after extraction on Sep-Pak cartridges, with a specific competitive radioimmuno-assay using the antiserum N1 (Theodorsson-Norhein 1985). Intra- and inter-assay coefficient of variance was 7 % and 11 %, respectively. Plasma NPY levels were compared with age adjusted reference levels (Kogner 1993).

Pharmacokinetic modelling

In paper I the pharmacokinetic data was analysed according to an open, two compartment model using a computerised pharmacokinetic least-square analysis (Davies 1977, Frisk-Holmberg 1978).

In papers II and IV the initial estimates for the pharmacokinetic modelling were obtained by the JANA stripping program (Dunne 1985). The final estimates of the pharmacokinetic parameters were obtained from the PC-Nonlin program (version 2.0) (Statistical Consultants 1986). The absorption process from the epidural space into the plasma compartment was evaluated according to Wagner-Nelson (Wagner 1964).

The optimal pharmacokinetic models were established by using F-ratio test (Boxenbaum 1974).

Haemodynamic measurements

Heart rate and non-invasive arterial blood pressure were recorded using a Hewlett-Packard Component Monitoring System (M1046-9001B; non-invasive blood pressure module M 1008B, ECG module M 1001 A) or a Propaq monitoring system (Propaq 106, Protocol Systems Inc, Oregon US).

Mathematical modelling of the haemodynamic response to intravenous clonidine

In study I the blood pressure response to intravenous administration of clonidine could be described by the following exponential equation: $MABP = A + B \times e^{-CT}$ (A = new baseline blood pressure, B = expected blood pressure drop, C = speed of blood pressure reduction). The constants A, B, and C were thereafter used for statistical analysis.

Analysis of heart rate and blood pressure variability

The effect of clonidine administration with regard to heart rate and systolic blood pressure variability was measured as the coefficient of variation (CV %) as described by Ghignone (Ghignone 1988) during the first 48 postoperative hours after an epidural co-infusion of clonidine and ropivacaine (Study VI).

Assessment of postoperative pain, sedation, delirium, shivering and POV

Postoperative analgesia was assessed by the Objective Pain Scale (OPS) (Norden 1991) in study IV and VII. Confusion was registered using a 4-point confusion scale (Aono 1997) in study VII. Sedation was assessed by a modification of The Vancouver Sedative Recovery

Scale (Macnab 1991) in study VII, and by a 3-point scale as described by Ivani et al (Ivani 1996) in study IV. Shivering and POV was recorded as present or absent during the recovery room period in study VII.

Parental questionnaire

In study VII parents were instructed to assess pain-relief, sedation, vomiting, and night sleep as an average score over 24 hours. In addition the parents were asked the following question regarding their preference concerning the postoperative behaviour of their child:

If you were able to choose the behaviour of your child during the first 24 postoperative hours, what would you prefer: A child that is calm and mostly sleeps during the first 24 hours or a child that is alert and ambulatory during the first 24 hours?

Statistical analyses

In study I the blood pressure drop was described according to the formula: $MABP = A + B \times e^{-CT}$ (A = new baseline blood pressure, B = expected blood pressure drop, C = speed of blood pressure reduction). The sign test was used to statistically analyse the overall blood pressure response. Paired Student´s t-test was used to test the heart rate response at three min post-injection.

Calculations of median values and non-parametric 95 % confidence intervals (CI) were based on Wilcoxon´s signed-rank test according to Tukey (Daniel 1978) in study II , III and IV.

A new statistical procedure for calculation of bioavailability (median and confidence intervals) with areas under the curve from two independent patient populations, one treated by the intravenous route and one treated by the extravascular route of administration, was based on Mann-Whitney statistics (study II, appendix 2). The calculations are similar to the Tukey procedure with geometric Walsh averages, used for calculation of the bioavailability of a cross over design. Data from all patients were tested by one- and two-compartment models preceded by first- and zero-order absorption process.

Changes in blood pressure and heart frequency were evaluated by Cusum plots (Wohl 1977) in study III.

Un-paired differences were evaluated by Pitman randomisation test based on the Mann-Whitney U-test (Dallal 1988) in studies III, IV and V.

The influence of clonidine on blood pressure and heart frequency, were established by the Fischer exact test in studies III and IV.

Influence of dose and plasma concentration of clonidine on blood pressure and heart frequency was studied by the Kendall´s independent test in paper III, IV and V.

Variations of blood pressure were analysed by Kruskal-Wallis analysis of variance in paper VI.

In paper VII, travel sickness, shivering, and confusion were calculated by Fisher´s exact test. OPS, sedation, and 24 hours follow up was calculated by Mann-Whitney Test. Vomiting was calculated by Mann-Whitney Test and Fisher´s exact test.

RESULTS

Excluded patients

Nine out of 238 patients were excluded from final analysis. In study I, one patient was excluded from the exponential modelling used to describe the blood pressure response to intravenous clonidine administration due to a linear blood pressure drop not fitting this model. Five patients in study VI were excluded due to inadequate epidural block or catheter dislocation. In study VII four patients were excluded for the following reasons: refusal to accept rectal premedication (n=1), major unexpected bleeding (n=1), development of severe bronchospasm following endotracheal intubation necessitating cancellation of surgery (n=1), and refusal to accept face mask induction (n=1). In study VII three children were excluded from the OPS evaluation due to pronounced restlessness causing errors in blood pressure measurements.

Study I

Pharmacokinetic part of the study

The obtained pharmacokinetic values are displayed in Table 8 together with comparable pharmacokinetic data in adults. The plasma concentration curve for clonidine in patient no. 2 is shown in Figure 8.

	Present study*	Lowenthal, Matzek & MacGregor† (review) 1988	Frisk-Holmberg, Paalzow & Edlund‡ 1981	Frisk-Holmberg, Edlund & Paalzow‡ 1978	Davies et al.§ 1977
Dose (μg·kg^{-1})	2.5	–	2.35 (0.51)	2.8 (–)	3.6 (–)
AUC (ng·ml^{-1}·min^{-1})	526 (93)	–	675 (80)	–	–
Distribution half-time (min)	11.8 (7.0) 8.9 (5.9–17.7)	–	–	2.6 (0.6)	10.8 (4.7)
Elimination half-time (h)	6.13 (1.33) 5.55 (4.60–7.63)	8–13	11.3 (1.8)	8.8 (1.5)	8.5 (0.9)
Vd (l·kg^{-1})	0.96 (0.43)	2.0	3.42 (0.40)	3.06 (–)	2.09 (0.19)
Total body clearance (ml·kg^{-1}·min^{-1})	4.85 (1.0)	3.60	3.48 (0.41)	3.99 (–)	3.05 (0.54)

AUC = Area under curve; Vd = volume of distribution.
* Half-lives: mean (SD) and harmonic mean (95% confidence interval); AUC, Vd, total body clearance: mean (SD).
† Elimination half-life: harmonic mean; Vd, total body clearance: mean.
‡ Mean (SD).
§ Mean (SEM).

Table 8. Pharmacokinetic data of clonidine after intravenous administration: children vs adults.
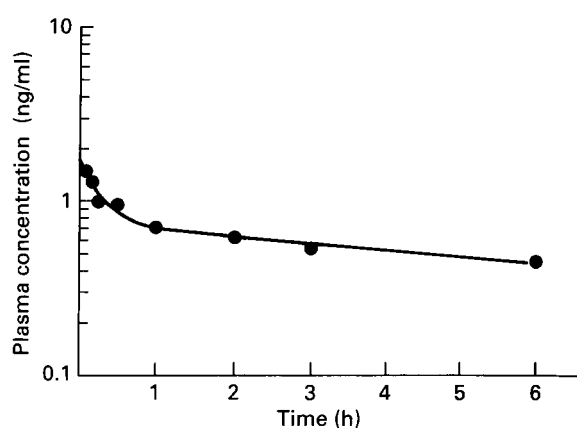
Figure 8. Plasma concentration-time curve for clonidine in patient no. 2.

Haemodynamic part of the study

A significant reduction in overall mean arterial blood pressure (MABP) was found in response to the clonidine injection (p = 0.003). The blood pressure response was best described according to the formula: MABP = A + B x e^{-Ct} (A = new baseline blood pressure, B = expected blood pressure drop, C = speed of blood pressure reduction)(Figure 9) The values for A, B, and C are shown in Table 9. A consistent finding in all patients was a harmonic undulation of the blood pressure response shown in Figure 9B.
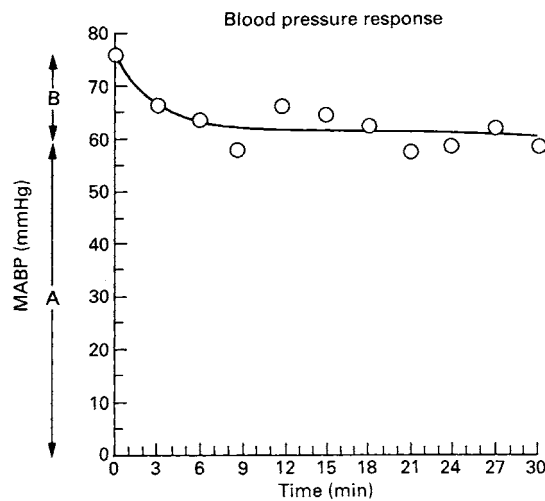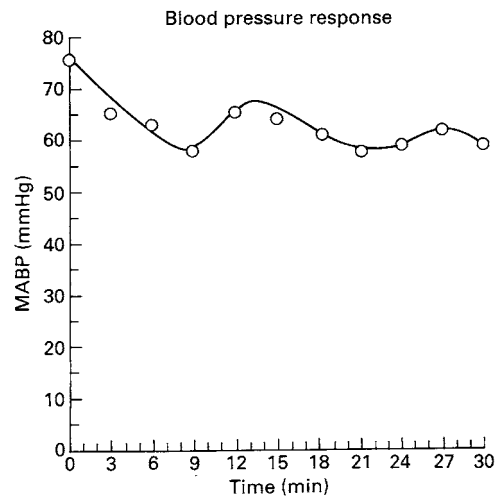
Figure 9. A. Blood pressure response after an intravenous clonidine injection (2.5 mcg kg^{-1}) in patient no. 1. The solid line represents the calculated blood pressure response.

B. Blood pressure response in patient no. 1(harmonic undulation). The solid line indicates a possible dampened sine wave response.

$$MABP = A + B \times e^{-CT}$$

	Mean	SD	95% CI
A	50.6	11.3	43.0–58.2
B	18.0	9.4	11.7–24.3
C	15.3	18.5	2.9–27.8

Table 9. Data regarding the blood pressure response after an intravenous injection of clonidine in children.

The magnitude of the blood pressure drop in relation to the initial blood pressure was found to be 26.3 % (SD: 13.6; 95 % CI: 17.2-35.4) The time for 75 % of the expected blood pressure drop to occur was on average 21.3 min (SD: 25.6; 95% CI: 4.1-38.5).

Three minutes post-injection a small but statistically significant reduction in heart rate could be detected (127 bpm (SD 19) *vs* 119 bpm (SD 20); p = 0.006). A gradual return to the pre-injection baseline values was subsequently observed and no further changes in heart rate could be noticed (Figure 10).
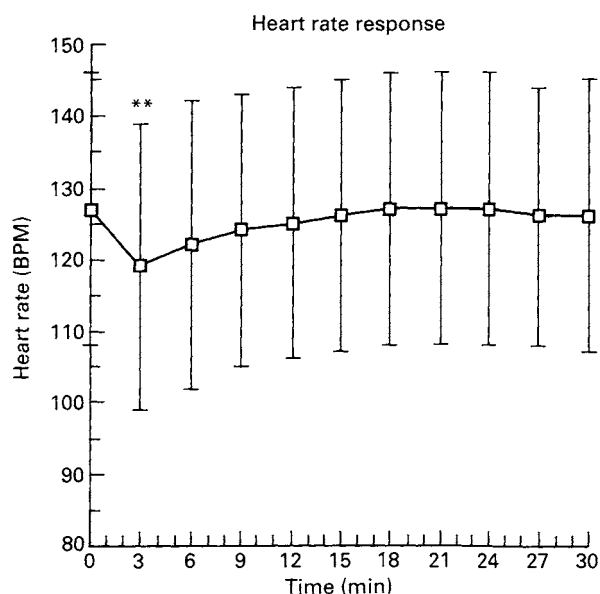
Figure 10. Mean (SD) heart rate response after an intravenous bolus injection of clonidine (2.5 mcg kg^{-1}) in children; ** p = 0.006.

Paper II

The median maximum plasma concentration after rectal administration of 2.5 mcg kg^{-1} was 0.77 ng mL^{-1} (95 % CI: 28.7-69.7) and the median time to obtain maximum plasma concentration was 52.1 min (95 % CI: 28.6-69.7 min). The median area under the curve for data from 0 to 24 hours was found to be 509 (95 % CI: 416-602). The plasma concentration patterns are illustrated in Figure 11. The median elimination rate constant was found to be 9.21 x 10^{-4} min^{-1} (95 % CI: 5.92-13.22 x 10^{-4}), corresponding to an elimination half-life of approximately 12.5 h. The rectal bioavailability was estimated to 95 % (95 % CI: 73-119).
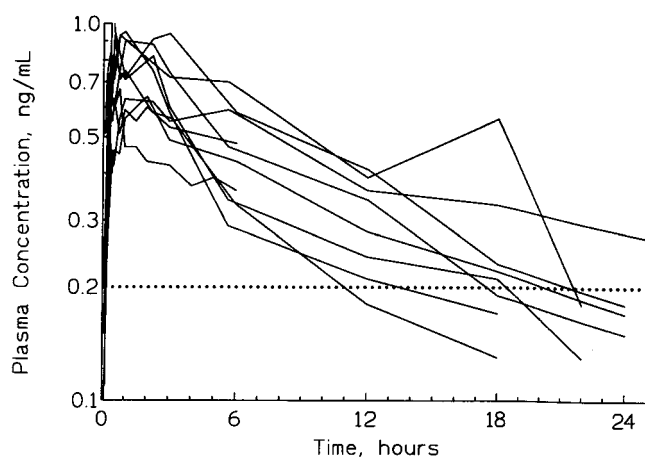
Figure 11. Plasma pharmacokinetics of rectal clonidine (2.5 mcg kg^{-1}) in children. Data from all patients are included. Dashed line = lowest reported plasma concentration associated with a clinical effect in adults (0.2 ng ml^{-1}).

Paper III

A decrease in mean arterial blood pressure (MABP) compared to baseline values was observed in all groups (Table 10). A significant reduction in MABP was seen in all groups receiving clonidine compared to control (Table 10). The relationship between plasma concentration of clonidine and blood pressure is shown in Figure 12.

Plasma concentrations of clonidine at 15 and 30 minutes post-injection were [median (95 % CI)] 0.38 ng mL^{-1} (0.22-0.69) and 0.24 ng mL^{-1} (0.21-0.31) in the study group receiving 0.625 mcg kg^{-1} and 0.76 ng mL^{-1} (0.49-1.04) and 0.53 ng mL^{-1} (0.36-0.79) in the study group receiving 1.25 mcg kg^{-1}. The heart rate was not significantly altered compared to baseline values in any of the groups.

Dose clonidine	MABP-reduction in % median	95% CI	P-value
control	8.62	5.21–11.29	
0.625 µg/kg	16.01	12.54–21.16	0.0016 (compared to baseline)
1.25 µg/kg	15.42	8.73–18.31	0.0415 (compared to baseline)

Table 10. Change in mean arterial blood pressure (MABP), per cent of baseline.
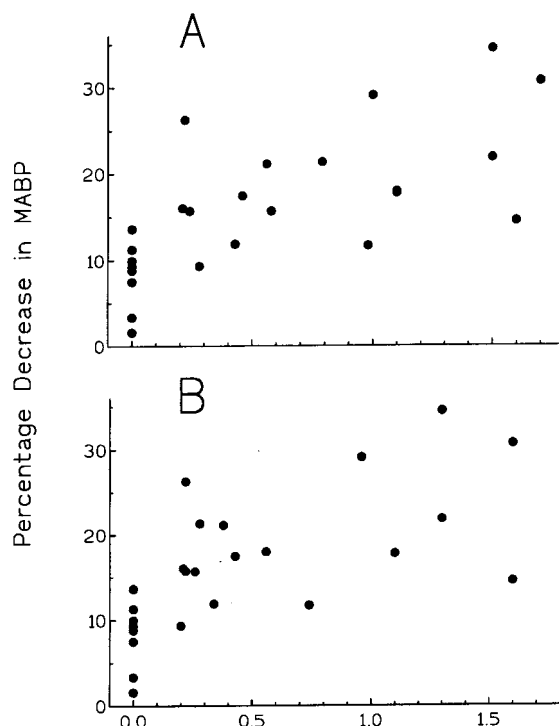
Figure 12. Change in mean arterial blood pressure (MABP) in relation to plasma concentration of clonidine. Panel A = 15 min, panel B = 30 min post injection. Note the MABP offset of approximately 10 % caused by general anaesthesia.

Paper IV

The plasma pharmacokinetics of clonidine following epidural administration showed a considerable interindividual variation (Figures 13 & 14, Table 11). C_{max} and T_{max} values of clonidine were found to be within the 0.45-0.77 ng mL^{-1} and 48-193 min range, respectively. The time to absorb 95 % of the clonidine dose from the epidural space into plasma varied between 36 minutes and 7.6 h. Despite this variability in absorption pattern the median bioavailability was estimated to 102 % (95 % CI: 87-146 %). All epidural blocks were judged to be successful due to the lack of haemodynamic reactions to the start of surgery.

Patient No.	Sex	Age year	Weight kg	AUC ng · min/mL	K_{10}-HL min	T_{max} min	C_{max} ng/mL	Time (h) to absorb 50%	Time (h) to absorb 95%	MRT min
1	Male	1	9	253	155	152	0.453	1.36	7.45	342
2	Male	1	10	424	181	193	0.676	1.66	7.64	387
3	Female	1	8.6	407	398	47.6	0.653	0.14	0.61	586
4	Male	1.5	13	428	421	133	0.599	0.21	1.59	553
5	Male	4	18	415	527	97.7	0.480	0.34	1.46	789
6	Female	9	41	600	479	73.8	0.772	0.10	1.05	707
7	Female	4	15	645	681	130	0.575	0.45	1.95	1021
8	Female	1.5	10	304	260	48.2	0.712	0.16	0.70	390
Median		1.5	11.5	423	396	108	0.620	0.34	1.65	578
95% CI				334–535	221–540	61.0–152	0.526–0.712	0.15–1.0	0.88–4.70	389–789

AUC=area under curve, K10-HL=elimination half-life time, T_{max}=time to maximum plasma concentration, C_{max}=maximum plasma concentration, MRT=mean residence time, CI=confidence interval.

Table 11. Demographic and pharmacokinetic data.
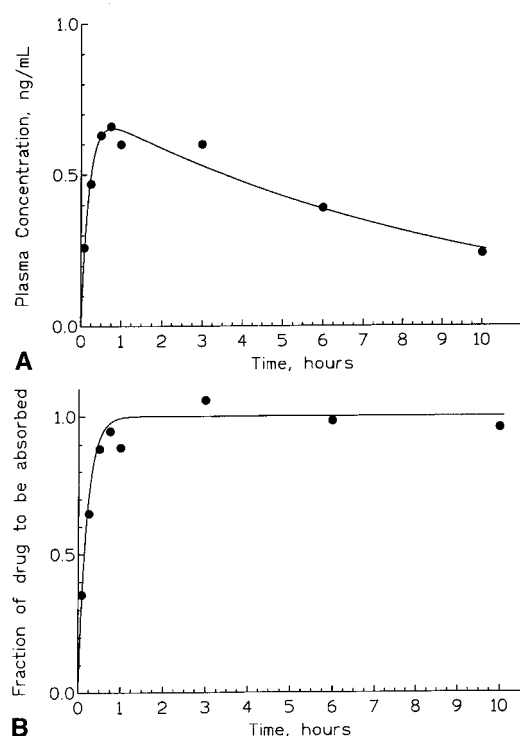
Figure 13. A. Clonidine plasma concentration-time relationship for a patient with a rapid absorption pattern (patient no. 3). **B.** Absorption-time relationship in the same patient.
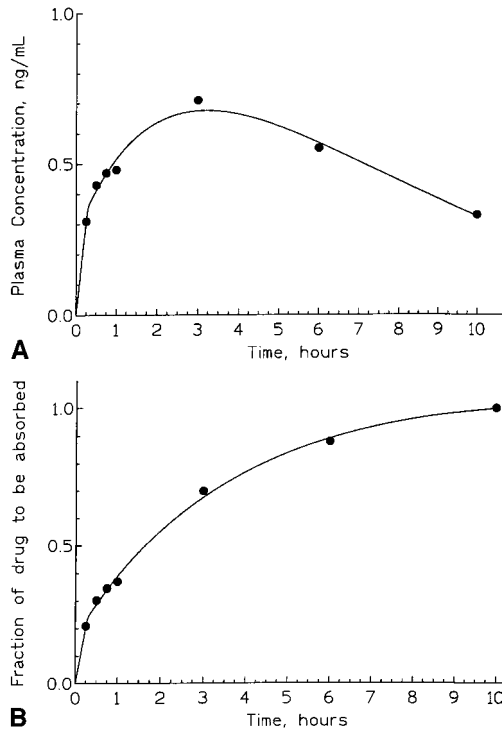
Figure 14. A. Clonidine plasma concentration-time relationship for a patient with a slow absorption pattern (patient no. 2). **B.** Absorption time relationship in the same patient.

The duration of postoperative analgesia and postoperative sedation are shown in Figure 15. In 6 of the 8 patients postoperative analgesia substantially outlasted the duration of sedation ($\geq$ 2 h). The relationship between plasma concentrations of clonidine and postoperative sedation is shown in Fig. 16. No correlation could be established between plasma clonidine concentrations and postoperative pain score.
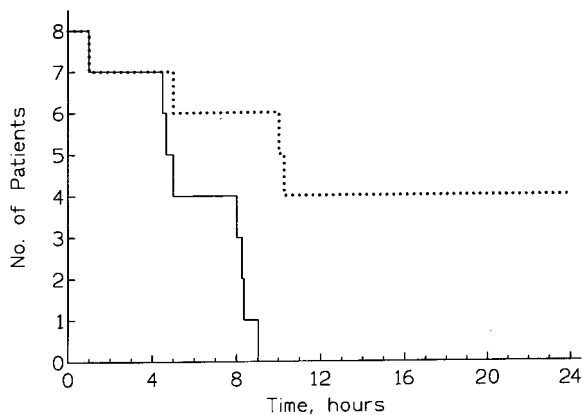
Figure 15. Postoperative sedation (solid line) and postoperative analgesia (dotted line) in relation to time. At 9 h postop no patient was scored to have residual sedation. At 24 h postop 4 patients still had no need for supplemental analgesia.

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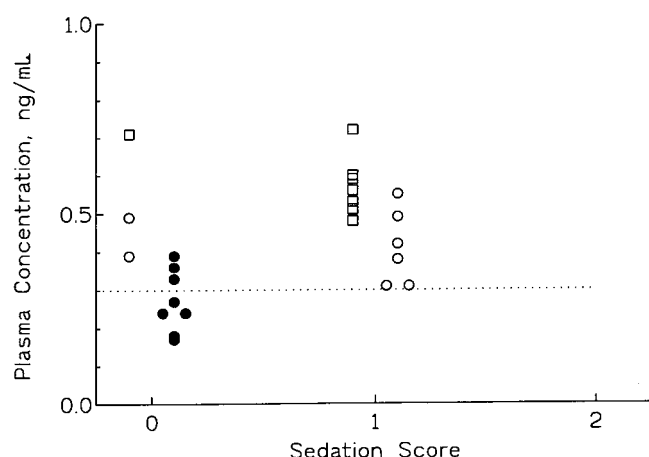
Figure 16. Relationship between plasma concentrations of clonidine and postoperative sedation score. Open squares = 6 h postop, open circles = 8 h postop, solid circles = 10 h postop. The dotted line indicates a possible clonidine plasma concentration threshold for postoperative sedation in children.

Paper V

Patients in the clonidine group were found to have a lower heart rate before intubation compared with patients receiving midazolam ($p < 0.05$)(Table 12). Haemodynamic state, NA and NPY responses after tracheal intubation are shown in Table 13. The NPY response after intubation did not change compared with baseline when the entire population was analysed together (Figure 17). The NPY response did not differ between the two subgroups (Table 13).

	Clonidine group	Midazolam group
Sex (F/M)	3/7	6/4
Age (months)	43.0 (37.0–57.0)	39.5 (25.5–59.0)
Weight (kg)	16.5 (14.5–18.0)	15.5 (13.5–17.3)
Heart rate (beat min^{-1})	113.5 (98.0–128.8)*	132.3 (120.8–144.0)
Mean arterial pressure (mm Hg)	65.5 (61.5–72.8)	68.0 (66.3–72.5)
Norepinephrine (nmol litre^{-1})	0.007 (0.005–0.100)	0.090 (0.065–0.130)
Neuropeptide Y (pmol litre^{-1})	21.0 (18.0–24.0)	21.0 (16.9–26.0)

Table 12. Baseline data, recorded immediately before induction of anaesthesia [median (95 % confidence limits)]. *P<0.05.

	Clonidine group				Midazolam group			
Time (min)	HR	AP	NE	NPY	HR	AP	NE	NPY
3	12.1 (5.3)	17.8 (3.8)	37.8 (13.0)	3.2 (8.2)	9.5 (1.6)	9.4 (2.3)	−0.7 (20.7)	−3.3 (10.7)
6	8.1 (3.9)	−1.4 (2.8)	44.6 (14.9)	10.8 (9.1)	9.4 (1.4)	−4.9 (4.5)	5.2 (17.5)	−1.8 (2.8)
9	7.1 (4.0)	−0.9 (3.3)	31.7 (14.3)	5.4 (8.9)	8.5 (2.0)	−3.2 (4.9)	7.2 (17.3)	2.5 (10.5)
12	7.0 (3.7)	−5.1 (2.2)	nd	nd	7.7 (2.0)	−7.3 (2.1)	nd	nd
15	6.4 (4.4)	−8.1 (1.8)	nd	nd	6.2 (2.2)	−8.5 (2.4)	nd	nd
18	6.8 (4.3)	−7.3 (2.0)	nd	nd	5.3 (2.4)	−10.8 (1.6)	nd	nd
21	6.2 (4.2)	−8.8 (1.9)	nd	nd	4.4 (2.5)	−10.0 (2.0)	nd	nd
24	7.4 (4.0)	−8.6 (2.3)	nd	nd	3.6 (2.6)	−11.6 (1.7)	nd	nd
27	7.4 (3.9)	−10.1 (2.4)	nd	nd	2.3 (2.7)	−10.4 (2.1)	nd	nd
30	8.7 (3.4)	−10.1 (2.7)	−9.8 (18.0)	2.0 (7.2)	1.4 (2.6)	−7.8 (2.7)	10.1 (13.2)	6.7 (16.1)

Table 13. Haemodynamic data, heart rate (HR), arterial pressure (AP), noradrenaline (NA), and neuropeptide Y (NPY) responses to tracheal intubation after clonidine or midazolam premedication. Data are mean (SEM) percentage change from pre-induction baseline values. nd = Not determined.
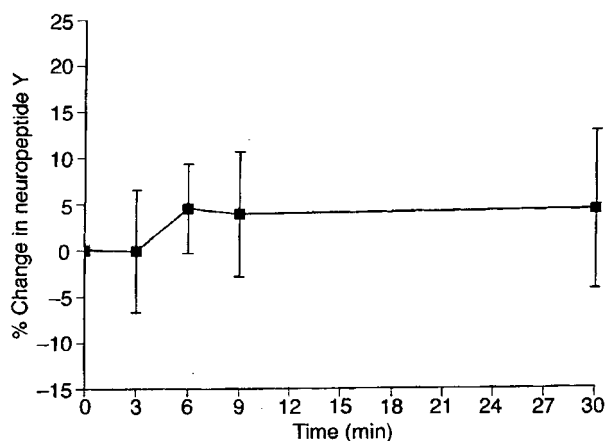
Fig 17. Percentage change in neuropeptide Y concentrations compared with baseline (whole study population).

Paper VI

No difference in overall heart rate or blood pressure levels could be detected between the four study groups. The variability of systolic blood pressure, measured as the coefficient of variance (CV) was found to be significantly lower in groups receiving clonidine 0.08 mcg kg-1 h-1 (RC2) (CV: 2.2 %) and clonidine 0.12 mcg kg-1 h-1 (RC3) (CV: 2.8 %) compared to patients receiving plain ropivacaine (R) (CV: 9.4 %) or clonidine 0.04 mcg kg-1 h-1 (RC1) (CV: 4.2 %) ($p < 0.001$) (Table 14, Figure 18). No difference was observed regarding heart rate variability.

	R	RC1	RC2	RC3	Kruskal-Wallis test
BP	9.37	4.24	2.24	2.75	P < 0.001
HR	5.54	5.09	5.99	5.47	P = 0.169

Table 14. Intrapatient variability of haemodynamic parameters. Data are presented as coefficient of variation (%)(median values). BP = non-invasive systoloic blood pressure, HR = heart rate.
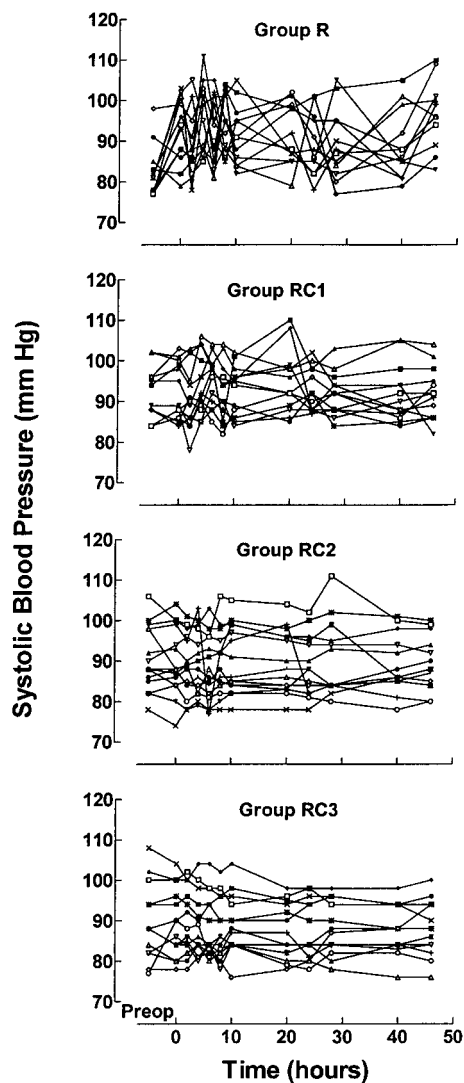

Figure 18. Individual systolic blood pressure recordings in patients receiving an postoperative epidural infusion of either plain ropivacaine 0.1 % (group R) or a co-infusion of ropivacaine 0.08 % and clonidine 0.12 mcg kg^{-1} h^{-1} (group RC3). Note the difference in individual variability and the lack of difference regarding overall blood pressure levels between the two groups.

Paper VII

Early postopeartive assessment (0-2 h)

OPS score: No difference in the individual OPS components could be detected between the two study groups, except for item VE/BL at 60 min. At this time point group C were found to have a higher proportion of patients with a score of zero compared to group M (p = 0.02). The total OPS score during the first two postoperative hours was significantly lower in group C compared to group M (p = 0.012) (Figure 19). The total OPS score was found to decrease with increasing total sedation score in both study groups (p < 0.001) (Figure 20). A similar magnitude of inverse relationship between total sedation score and total OPS score was observed in both study groups as indicated by the R_s values (Group C: R_s = -0.603 (95%CI: -0.763 — -0.375); Group M: R_s = -0.467 (95%CI: -0.667— -0.206)).
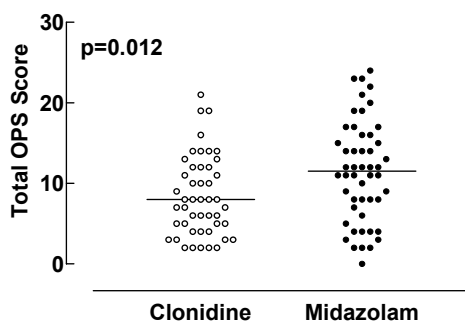
Figure 19. Total OPS score. Median values are given by the solid lines.
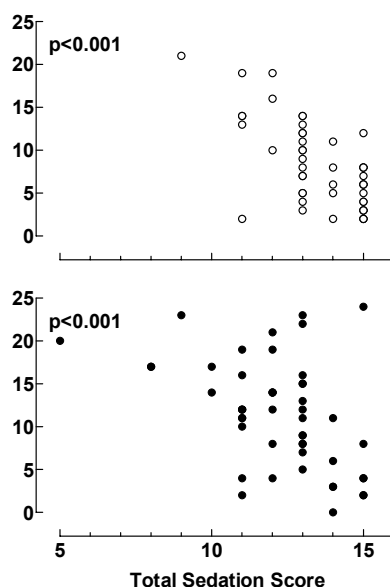
Clonidine=Open symbols: R_s = -0.603 (95 % CI: -0.763 - -0.375)
Midazolam=Closed symbols: R_s = -0.467 (95 % CI: -0.667 - -0.206)

Figure 20. Total OPS score *vs.* total sedation score. Open symbols = clonidine, solid symbols = midazolam.

Sedation: Patients in group C were found to have a higher total sedation score compared to patients in group M ($p < 0.001$). However, the numeric difference in median values was small (group C: 13; group M: 12).

Confusion: The confusion score in the clonidine and midazolam treated children did not differ ($p = 0.15$). A higher incidence of confusion could, however, be observed in boys compared to girls (median values 8 and 6, respectively; $p = 0.018$). The confusion score was found to be lowest in girls belonging to group C. Immediately after the anaesthetic 31 % of patients in group C and 42 % of patients in group M suffered from delirium ($p = 0.30$).

Shivering: No occurrence of shivering was recorded in group C whereas shivering was observed in 5 patients in group M ($p = 0.057$).

Vomiting: Six patients in group C and 13 patients in group M did vomit during the first two postoperative hours ($p = 0.22$). Only two children needed anti-emetic rescue medication with dixyrazin.

24-h follow-up

Parental 24 hour evaluation: There was no difference in the incidence of vomiting ($p = 0.61$), postoperative pain evaluation ($p = 0.76$), number of paracetamol doses ($p = 0.55$) or night sleep pattern ($p = 0.99$) between the two study groups following discharge from the hospital. Children treated with clonidine had a lower sedation score, i.e. were more sedated than children in the midazolam group ($p = 0.024$).

Parental preference of postoperative behaviour: 75 % of parents preferred a sedated and mostly sleeping child compared to an alert and ambulating child during the first 24 postoperative hours (Figure 21) ($p < 0.001$).
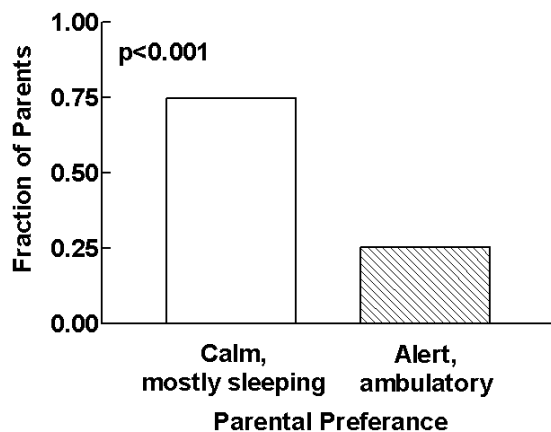

Figure 21. Parental preferences of children behaviour during the first 24 hours.

GENERAL DISCUSSION

Pharmacokinetics of clonidine in children

The pharmacokinetic profile of clonidine in adults has previously been studied in detail (Frisk-Holmberg 1978, Frisk-Holmberg 1981, Lowenthal 1988, Davies 1977) but very limited information on paediatric pharmacokinetics was to our knowledge available prior to the investigations that form part of this dissertation. A primary aim of the present thesis was, thus, to provide such information in order to allow the safe use of this drug in children. As a result of our studies we can now conclude that regardless of the different routes of administration used in our studies, regular pharmacokinetic parameters in children only differ marginally from adult values.

The slight difference between study I and II regarding the terminal half-life of clonidine is likely explained by the limited sampling period in the first study, leading to a moderate underestimation of the elimination half-life in study I. It should, however, be noted that we have not studied the pharmacokinetics of clonidine in children less than one year of age and that further pharmacokinetic investigations are necessary in this patient category.

In order to allow the determination of bioavailability in our paediatric populations a new statistical procedure for calculation of bioavailability based on median and confidence intervals for the areas under the curve from two independent patient populations, one treated by the intravenous route and one treated by an extravascular route of administration (rectal route- study II, epidural route- study V) was constructed (study II, appendix 2). Using this new method almost complete bioavailablility was found for epidurally administered clonidine (study V). The rectal bioavailability of clonidine in children was found to be 95 %, a figure that closely corresponds to the oral bioavailability found in adults (Davies 1977, Arndts 1983). Rectal clonidine premedication was also found to achieve plasma concentrations associated with the onset of pharmacodynamic effects seen in adults (Lowenthal 1988) after approximately 20 minutes and peak plasma concentrations were reached approximately 50 minutes after rectal administration. This pharmacokinetic profile of rectally administered clonidine combined with a high patient compliance for this route of administration in the studied patient populations (patient or parental rejection rate less than 1 %) indicate that this route of administration would be an acceptable alternative to other currently used premedication techniques in Scandinavian children.

Pharmacodynamics of clonidine in children

Since clonidine is a drug know to reduce systemic blood pressure a further aim of the dissertation work was to define the blood pressure reaction to clinically relevant doses for paediatric use. This was done in order to ascertain whether the haemodynamic response to clonidine in children was in fact acceptable from a safety stand-point.

The blood pressure reduction recorded after intravenous clonidine administration (2.5 mcg kg$^{-1)}$) during unstimulated isoflurane anaesthesia was found to be of moderate magnitude (26 %) (study I) and approximately half of this reduction could be explained by the effect of the isoflurane anaesthesia *per se*, as illustrated by the placebo group in study III. The lack of a plasma concentration dependent blood pressure effect in the lower clonidine dose range reported in study III can be taken to indicate that this dose range represents a part of the initial lower, more flat part of the dose-response curve.

Clonidine has previously been reported to reduce absolute heart rate and blood pressure as well as heart rate and blood pressure variability in adults (Akselrod 1985, Baselli 1986, Saul 1991, Cloarec-Blachard 1997, Quintana 1997). Despite these effects the baroreceptor reflex appears to be left intact after clonidine administration and the blood pressure is merely re-set at a lower level (Badoer 1983). In our first study we could in some patients observe a variability in the pattern of the initial blood pressure reduction that potentially could be described as a dampened sine wave response (study I, Figure 9B). Upon further analysis some form of blood pressure variability could be detected. However, we were unable to establish any mathematical model that could adequately describe this phenomenon (data not shown).

We also decided to focus on the effects on the postoperative heart rate and blood pressure variability during the adjunct administration of clonidine to a continuous epidural infusion of ropivacaine in children (study VI). No effect was noted with regard to the overall heart rate and blood pressure levels but the administration of clonidine at approximately 0.1 mcg kg^{-1} h^{-1} was found to significantly reduce the blood pressure variability during the first 48 postoperative hours. This finding could be explained by the superior analgesia associated with this infusion rate of clonidine (De Negri 2001 A) but could also represent a direct effect of clonidine on the cardiovascular system or the vasomotor centre in the brain stem.

Despite the finding of a reduced postoperative variability in postoperative blood pressure associated with epidural clonidine-ropivacaine infusion no effect was seen with regard to heart rate variability. This is in contrast to what has been described in adults where a reduction in both heart rate and blood pressure variability is seen in the postoperative phase

(Parlow 1999). The reason for this discrepancy between children and adults can not be determined from our recorded data but deserve further investigation.

With regard to the overall effect on heart rate caused by a bolus injection of clonidine during anaesthesia a transient but clinically insignificant initial reduction in heart rate could be observed. It should, however, be noted that the subjects in our studies had received premedication with atropine that potentially could have masked a more pronounced effect on the heart rate. Later studies published by other authors have not been able to reproduce this transient reduction in heart rate after clonidine administration in children (Mikawa 1995 A, Nishina 1996, Klimscha 1998), possibly due to differences in study design. Based on these later studies and in order not to interfere with the heart rate variability we excluded atropine when studying the variability of heart rate and blood pressure in study VI.

We want to emphasise that we have only studied clonidine in doses up to 5 mcg kg^{-1} and are, thus, not able to make any prediction on the haemodynamic effect of doses in excess of this dose interval. However, in adults a biphasic dose-response relationship exists to clonidine (Jarvensivu 1984, Eisenach 1996). At doses in the 0-10 mcg kg^{-1} dose range a dose dependent blood pressure reduction occurs but at doses in excess of approximately 10 mcg kg^{-1} the blood pressure will start to increase and can reach hypertensive levels, possibly due to a direct effect on vascular alpha-1 and postsynaptic alpha-2 adrenoceptors at these high dose levels (Jarvensivu 1984, Eisenach 1996). Thus, clonidine does appear to have a built in haemodynamic safety mechanism and as a result seems to be associated with a broad safety margin. This is further supported by the lack of mortality reports in the literature following clonidine poisoning in toddlers (Anderson 1981, Artman 1983, Olsson 1983, Fiser 1990, Wiley 1990, Maloney 1995). Further indications of the potential safety of clonidine is illustrated by a recent case report where a thousand fold unintentional overdose in a 5 year old child did not result in any long-term sequele (Romano 2001). The haemodynamic stability associated with clonidine is also illustrated in a recent study by Ambrose et al where postoperative infusions of clonidine within the 0.1-2.0 mcg kg^{-1} h^{-1} were associated with a dose related increase of sedation but where without any major effects on haemodynamics after cardiac surgery in children (Ambrose 2000).

Clinical effects of clonidine in children

Mikawa and colleagues have previously demonstrated a slight but statistically significant attenuation of the haemodynamic response to tracheal intubation in older children after oral

premedication with 4 mcg kg^{-1} of clonidine compared with oral diazepam (Mikawa 1995). In our study (IV) when comparing rectal clonidine premedication 2.5 mcg kg^{-1} with rectal midazolam 0.3 mg kg^{-1} we were unable to identify any increase in NPY plasma concentrations after a standardised intubation procedure performed during light isoflurane anaesthesia. Neither could any significant difference in NPY release be detected between the clonidine and the midazolam group. The discrepancies between our results and the results reported by the Kobe group might be a result of different doses of clonidine, a difference in age between the study populations or different actions in this regard between various bensodiazepine drugs. However, based on our findings we conclude that the stress response to endotracheal intubation in children is short lived and of limited magnitude, as indicated by the lack of NPY release. Routine administration of drugs (e.g. opioids) to attenuate this transient response to endotracheal intubation in otherwise healthy children does, thus, not appear necessary.

There are numerous studies in adults showing an analgesic effect of clonidine (Fleetwood-Walker 1985, Xie 1986, Hall 2001) and this analgesic effect of clonidine has also been reported in a number of studies in children (Nishina 1996, Nishina 1997). It has been suggested that the central analgesic action of systemically administrated alpha-2 adrenoceptor agonists is mediated by its sedative properties by decreasing the unpleasantness of the pain experience (Priddle 1950). This hypothesis represents an important issue from an academic point of view since a common problem with paediatric pain scales is the possible interference caused by concomitant sedation on pain assessments (McGrath 1985). The significant reduction in overall postoperative OPS scores after rectal clonidine compared to midazolam seen in study VII, thus, require further consideration. This is further highlighted by the finding of a significant inverse relationship between sedation and the OPS score in study VII. However, no difference in the inverse relationship between sedation and OPS score could be detected between the patients treated with clonidine and those treated with midazolam. Against this background we conclude that the observed difference between the study groups regarding early postoperative pain most likely represents a valid observation and not only an effect that can be related to concomitant sedation. Furthermore, the observations made in study V appear to support this interpretation since postoperative analgesia substantially outlasted postoperative sedation in 6 out of 8 patients in this study, suggesting that concomitant sedation is not a major factor influencing the postoperative analgesia seen after

epidural administration of clonidine. However, the relationship between sedation and analgesia after clonidine needs to be confirmed by further placebo controlled studies.

A major objective in out-patient surgery in adults is rapid recovery and early ambulation in order to facilitate discharge from the hospital. This is important in order to increase turnover and thereby improve the cost-effectiveness of ambulatory surgery. Thus, a key factor in adult out-patients is the ability to cope without assistance from hospital staff or relatives. However, this is not the situation following paediatric ambulatory surgery since the child is always accompanied by the parents or other caregivers. It has even been suggested by Lerman that a certain degree of residual sedation in the early postoperative phase might represent a desired effect by the parents (Lerman 2000). In order to further elucidate this issue we incorporated a postoperative follow-up regarding parent preference regarding their child's behaviour in study VII. In this 24 hours follow-up we could demonstrate that children treated with clonidine were significantly more sedated than children in the midazolam group. However, a substantial majority of parents (75 %) in fact preferred a sedated and sleepy child compared to an alert and ambulatory child during the first 24 postoperative hours. These results confirm the notion that the moderate postoperative sedation caused by clonidine in fact should be regarded more as an addition beneficial effect than an unwanted side effect in children.

In a recent study we have been able to show that clonidine administration is associated with a reduced incidence of PONV following breast cancer surgery (Oddby 2002), a study that was inspired by the report of reduced PONV after strabismus surgery in children treated with clonidine as a premedicant (Mikawa 1995 B). Although the incidence of vomiting was two-fold higher in the midazolam group as compared to the clonidine group during the recovery room period in study VII this difference was not statistically significant. The most likely reason for this finding not reaching statistical significance is that study VII was under-powered in this regard since PONV was not the primary end-point of the study.

Clonidine administration has been reported to decrease the incidence of postoperative shivering (Buggy 1997) and to be an effective alternative in the treatment of already establish shivering (Mercandante 1994) in adults. Data regarding the effect on postoperative shivering has to our knowledge not previously been reported in children. In study VII data regarding the incidence of postoperative shivering was thus collected. None of the patients treated with clonidine was found to shiver in the early postoperative period, whereas 11 % of the patients

in the midazolam group were observed to shiver during the recovery room stay. Although this difference did not quite reaching statistical significance this trend for less shivering following clonidine administration merits further study.

Clonidine vs. Midazolam as premedication

Midazolam is currently maybe the most widely used drug for premedication and sedation in children. The reason for its popularity is somewhat obscure since the published scientific documentation is far from conclusive regarding its superiority compared to other alternatives in children. The present popularity can in the author's opinion to a large extent be attributed to aggressive and successful marketing of the drug. Midazolam does posses certain merits in the context of premedication but its cost and the risk for prolonged postoperative behavioural problems (McGraw 1998) should be taken in to consideration. Furthermore the ability to produce amnesia is dubious. Many clinicians are of the option that the amnesic effect seen with midazolam is a major advantage. However, the amnesic effect is perhaps not an effect that is readably appreciated by the patient. A period of loss of memory or blurred memory is frequently experienced as quite distressful in adults and there is no data indicating that this would be different in the paediatric population. It can be argued that even if the memory of a procedure is unpleasant it could nevertheless be preferable to a period of black-out. Since the sedation caused by alpha-2 adrenoceptor agonist produces a more sleeplike situation (Hall 2001) from which the patient easily can be awakened this might be preferable in the perioperative setting. Also the ability to retain memories can be an additional advantage. In the authors opinion further investigations with regard to these aspects are clearly warranted.

In one of the two prospective, randomised, double-blind trials that form part of this dissertation clonidine was found to be superior compared to midazolam following adeno-tonsillectomy with regard to early postoperative pain, the primary end-point of the study (study VII). However, in a recent study Fasi and co-workers reported that children premedicated with oral clonidine (4 mcg kg^{-1}) had higher pain scores and opioid requirements in the early postanaesthetic period compared to oral midazolam in paediatric tonsillectomy patients (Fazi 2001). The reason for the diverging findings of that study in comparison with the results form study VII is not clear but at least one issue needs to be addressed more in detail. The difference in bioavailablility between oral (27-36%) (Payne 1989, Reed 2001) and rectal (16-18%)(Kraus 1989) administration of midazolam and the difference in midazolam dose used in the study published by Fasi et al (0.5 mg kg^{-1}) and the dose used in study VII

(0.3 mg kg^{-1}) could be expected to produce at least three times higher plasma concentration of midazolam in the study by Fasi and co-workers compared to study VII. Thus, the better pain relief in the midazolam group observed by Fasi et al could possibly reflect a more pronounced degree of postoperative sedation, since the CHEOPS pain scale used in that study is known to be highly influenced by concomitant sedation (McGrath 1985). Their finding of significantly faster emergence from anaesthesia in the clonidine group compared to the midazolam group is a further support for this interpretation. Despite the slight increase of sedation during the recovery room stay in the clonidine group in study VII, a similar magnitude of inverse relationship between sedation and pain score was observed in patients receiving clonidine or midazolam (Figure 20). Thus, the present study is better adjusted for any interference from sedation with pain assessments made with a behavioural based pain scale as compared to the study by Fasi et al.

Final remark

In the seven studies that form the basis for this dissertation the haemodynamic response after clonidine administration was found to be of a clinically acceptable magnitude and should be well tolerated in otherwise reasonably healthy children. The pharmacokinetic parameters after intravenous, rectal, and epidural administration were similar to those reported in adults. Thus, we conclude that there are no pharmacokinetic or haemodynamic aspects that should restrict the use of clonidine within the dose range 1-5 mcg kg^{-1} in children 1-10 years of age.

The use of rectal clonidine was associated with a significant reduction of pain scores during the early postoperative period after adeno-tonsillectomy when compared to midazolam. The use of clonidine is also associated with slightly increased sedation ratings during the first 24 postoperative hours compared to midazolam. However, this effect on sedation is in agreement with the unequivocal parental preference of a calm and sedated child during the early post-operative time period. Based on our own results, as well as data published by other research groups, we conclude that clonidine represents a safe and useful pharmacologic alternative in paediatric anaesthesia.

CONCLUSIONS

Based on data generated from the seven studies of the present dissertation we would like to make the following conclusions:

1. A shorter terminal half-life, a smaller volume of distribution and a higher total body clearance is found in children after intravenous clonidine administration when compared with previously reported adult data. After rectal administration the elimination half-life was similar to that described in adults.

2. Following epidural administration of clonidine the pharmacokinetic profile in children is similar to that described in adults. However, a substantial interindividual variability in the absorption pattern of epidural clonidine exists.

3. Rectal administration of clonidine is associated with high bioavailability (95%). The median time to obtain maximum plasma concentration is approximately 50 minutes.

4. The observed blood pressure reduction after administration of 2.5 mcg kg^{-1} of intravenous clonidine during light isoflurane anaesthesia is of a moderate magnitude.

5. No clear dose-response relationship with regard to blood pressure reduction is present after intravenous administration of clonidine within the dose range 0.625-2.5 mcg kg^{-1}.

6. In paediatric patients the postoperative analgesic effect of epidural clonidine frequently outlasts the duration of postoperative sedation by more than 2 hours.

7. The stress response associated with endotracheal intubation during light isoflurane anaesthesia is associated with substantial interindividual variation in children. However, the response is short-lived and only of a minor-moderate magnitude as indicated by the lack of NPY release.

8. Rectal premedication with clonidine 2.5 mcg kg^{-1} does not attenuate the stress response associated with endotracheal intubation compared to rectal administration of midazolam 300 mcg kg^{-1}.

9. Adding a continuous epidural infusion of clonidine in doses of $\geq$ 0.8 mcg kg^{-1} h^{-1} to an epidural infusion of ropivacaine results in reduced blood pressure variability in the postoperative period in children.

10. The use of rectal clonidine 5 mcg kg^{-1} as premedication significantly reduces early postoperative pain after adeno-tonsillectomy in children compared to midazolam.

11. In children clonidine administration is associated with slightly more pronounced postoperative sedation compared to midazolam. However, this sedative effect of clonidine is in agreement with a distinct parental preference for a calm and sedated child during the first 24 postoperative hours.

ACKNOWLEDGEMENTS

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