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Studies on Pediatric and Adult Patients, and Healthy Adult Volunteers

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University of Turku

Faculty of Medicine
Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
Drug Research Doctoral Programme
Perioperative Services, Intensive Care and Pain Medicine
Turku University Hospital

Supervised by

Associate Professor Teijo Saari, MD, PhD
Department of Anesthesiology
and Intensive Care, University of Turku,
and Turku University Hospital
Turku, Finland

Professor Mika Scheinin, MD, PhD
Institute of Biomedicine,
University of Turku, and
Turku University Hospital
Turku, Finland

Reviewed by

Docent Kai Kiviluoma, MD, PhD
Department of Anesthesiology and
Intensive Care, University of Oulu, and
Oulu University Hospital
Oulu, Finland

Professor Mikko Niemi, MD, PhD
Department of Clinical Pharmacology,
University of Helsinki, and
Helsinki University Hospital
Helsinki, Finland

Opponent

Professor Arvi Yli-Hankala
Department of Anesthesiology and
Intensive Care, University of Tampere, and
Tampere University Hospital
Tampere, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Cover Image: Elina Uusalo

ISBN 978-951-29-7774-1 (PRINT)
ISBN 978-951-29-7775-8 (PDF)
ISSN 0355-9483 (Painettu/Print)
ISSN 2343-3213 (Sähköinen/Online)
Painosalama Oy – Turku, Finland 2019

To Anna-Leena and Eino

ABSTRACT

Panu Uusalo

Pharmacokinetics and effects of extravascularly administered dexmedetomidine

Studies on Pediatric and Adult Patients, and Healthy Adult Volunteers

University of Turku; Faculty of Medicine; Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine; Drug Research Doctoral Programme; Perioperative Services, Intensive Care and Pain Medicine; Turku University Hospital

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2019

Patients undergoing surgery and other invasive procedures need sedation and pain relief. Many unpleasant sensations and experiences can be reduced by administration of conventional sedative and analgesic drugs, but most of these compounds are associated with troublesome adverse effects such as respiratory depression and nausea.

Dexmedetomidine is a relatively new drug that acts by activating α_2-adrenoceptors. It has received marketing authorisation for intensive care sedation and for procedural sedation of adult patients. In addition to its sedative property, dexmedetomidine exerts analgesic and antiemetic effects. In comparison to other analgesic and sedative agents, dexmedetomidine has minimal effects on respiration.

Dexmedetomidine has been developed and approved for intravenous administration. Several reports exist on the use of intranasal and other extravascular routes of administration of dexmedetomidine. Nonetheless, the pharmacokinetic and pharmacodynamic properties of extravascularly administered dexmedetomidine have remained poorly characterized. The intranasal route of administration appears to be feasible for administration of dexmedetomidine to children, but there is rather little information available about the pharmacokinetics of dexmedetomidine in children.

In the present series of studies, the pharmacokinetics and -dynamics of subcutaneously and intranasally administered dexmedetomidine were characterized in healthy volunteers and in pediatric patients. We also evaluated the anesthetic sparing effect of intranasally administered dexmedetomidine in pediatric patients undergoing ambulatory sedation, and the analgesic sparing effect of intranasally administered dexmedetomidine in adult patients undergoing hip arthroplasty under general anesthesia.

The systemic bioavailability of subcutaneously administered dexmedetomidine was good (81%), but interindividual variation was large. After intranasal administration of dexmedetomidine in pediatric patients, on average the peak plasma concentrations were achieved in 37 minutes, with peak effects normally observed at 45 minutes. Peak concentrations and exposure to the study drug decreased with age. Intranasal doses of 2-3 μg/kg achieved clinically acceptable sedation in about 94% of pediatric patients undergoing magnetic resonance imaging. In adult patients undergoing total hip arthroplasty, the use of intranasal low-dose dexmedetomidine decreased postoperative opioid consumption in a clinically significant manner.

Our findings provide support for the use of intranasal dexmedetomidine in pediatric patients requiring light or moderate sedation and in adult patients undergoing painful surgical procedures. Subcutaneous administration of dexmedetomidine appears promising e.g. for patients needing palliative sedation and analgesia, but further studies are warranted to confirm this proposal.

Keywords: dexmedetomidine, subcutaneous, intranasal, pharmacokinetics, pharmacodynamics

TIIVISTELMÄ

Panu Uusalo

Ekstravaskulaarisesti annostellun deksmedetomidiinin farmakokinetiikka ja vaikutukset

Tutkimuksia aikuis- ja lapsipotilailla sekä terveillä vapaaehtoisilla aikuisilla

Turun yliopisto; Lääketieteellinen tiedekunta; Anestesiologia ja Tehohoito; Lääketutkimuksen tohtoriohjelma; Toimenpide-, tehohoito- ja kivunhoitopalvelut, Turun yliopistollinen keskussairaala

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2019

Leikkauksiin ja muihin toimenpiteisiin tulevat potilaat tarvitsevat rauhoittavaa ja kipua lievittävää lääkitystä. Vaikka monia epämiellyttäviä oireita ja tuntemuksia voidaan lievittää tavanomaisilla kipu- ja rauhoittavilla lääkkeillä, liittyy niiden käyttöön usein hankalia haittavaikutuksia kuten hengityslamaa ja pahoinvointia.

Deksmedetomidiini on uudehko aikuisten tehohoito- ja toimenpidepotilaiden rauhoittamiseen myyntiluvan saanut, α_2-adrenoseptoreja aktivoiva lääkeaine, jolla on väsyttävä ja potilasta rauhoittava vaikutus, mutta lisäksi myös kipua ja pahoinvointia lieventäviä vaikutuksia. Deksmedetomidiinin etu verrattuna tavanomaisiin kipu- ja rauhoittaviin lääkkeisiin on sen hyvin vähäinen vaikutus potilaan hengitykseen.

Deksmedetomidiini on kehitetty ja tarkoitettu annosteltavaksi laskimoon. Monia muitakin annostelureittejä, kuten annostelua nenän limakalvoille, on tutkittu. Deksmedetomidiinin annostelusta muuten kuin laskimon kautta on tehty kuitenkin vain vähän farmakokineettisiä ja farmakodynaamisia tutkimuksia. Vaikka annostelua nenän limakalvolle käytetäänkin jo lapsipotilailla varsin usein, ei sen imeytymistä ja käyttäytymistä elimistössä ole lapsipotilailla juurikaan tutkittu.

Tässä tutkimussarjassa verrattiin ihon alle ja laskimoon annostellun deksmedetomidiinin farmakokinetiikkaa ja -dynamiikkaa terveillä vapaaehtoisilla aikuisilla sekä tutkittiin nenän limakalvoille annostellun deksmedetomidiinin farmakokinetiikkaa ja -dynamiikkaa lapsipotilailla. Tutkimme lisäksi nenän limakalvoille annostellun deksmedetomidiinin vaikutusta nukutuslääkkeen tarpeeseen sedaatiota tarvitsevilla lapsipotilailla sekä yleisanestesiassa tehdyn lonkkaproteesileikkauksen jälkeiseen kipulääkkeen tarpeeseen aikuispotilailla.

Ihon alle annostellun deksmedetomidiinin hyötyosuus osoittautui hyväksi (81 %), mutta yksilöiden välinen vaihtelu oli suurta. Lapsipotilailla nenän limakalvoille annostellun deksmedetomidiinin huippupitoisuus plasmassa saavutettiin 37 min ja huippuvaikutus 45 min kuluttua lääkkeen annostelusta. Huippupitoisuus ja altistus lääkkeelle pienenivät iän myötä. Nenän limakalvoille annosteltu deksmedetomidiini aiheutti merkittävän sedaation annoksella 2-3 μg/kg. Aikuispotilailla nenän limakalvoille annosteltu pieniannoksinen deksmedetomidiini vähensi leikkauksen jälkeisen opioidikipulääkkeen tarvetta.

Löydöksemme kannustavat käyttämään nenän limakalvoille annosteltua deksmedetomidiinia lapsipotilailla, jotka tarvitsevat kevyttä tai kohtalaista sedaatiota, sekä aikuispotilailla, joille tehdään kivuliaita leikkauksia. Myös ihon alle annosteltu deksmedetomidiini vaikuttaa lupaavalta esim. palliatiivista hoitoa saaville potilaille, mutta annostelusta tarvitaan lisää kliinisiä tutkimuksia.

Avainsanat: deksmedetomidiini, ihonalainen, intranasaalinen, farmakokinetiikka, farmakodynamiikka

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ABBREVIATIONS

AE	adverse event
ASA	American Society of Anesthesiology
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
BMI	body mass index
bpm	beats per minute
cAMP	cyclic adenosine 3,5-monophosphate
CBSS	Comfort-B sedation scale
CL	plasma clearance
C_{max}	peak concentration in plasma
CO	cardiac output
CRF	case report form
CYP	cytochrome P450
ECG	electrocardiography
EEG	electroencephalogram
F	bioavailability
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GOF	goodness-of-fit
G-protein	guanine nucleotide binding protein
HR	heart rate
ICU	intensive care unit
IQR	interquartile range
MAP	mean arterial pressure
MRI	magnetic resonance imaging
nREM	non-rapid eye movement
NSAID	non-steroidal anti-inflammatory drug
OFV	objective function value
PK/PD	pharmacokinetic/pharmacodynamic
PACU	post anesthesia care unit
SE	state entropy
SD	standard deviation
SpO_2	arterial oxyhemoglobin saturation measured by pulse oximetry
$t_{1/2}$	elimination half-life
T_{max}	time to peak concentration

TCI	target-controlled infusion
VAS	visual analogue scale
V_{ss}	volume of distribution at steady state
V_1	volume of the central compartment
V_2	volume of the rapid compartment

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which will be referred to in the text by the Roman numerals I – V.

I Uusalo P, Tilli I, Al-Ramahi D, Aantaa R, Scheinin M, Saari TI. Pharmacokinetics and bioavailability of subcutaneous dexmedetomidine in healthy adult volunteers. Eur J Clin Pharmacol. 2018; 74(8):1047-1054.

II Ashraf MW, Uusalo P, Scheinin M, Saari TI. Semi-mechanistic population pharmacokinetic-pharmacodynamic model of intravenous and subcutaneous dexmedetomidine in healthy human volunteers. *Submitted manuscript*.

III Uusalo P, Guillaume S, Sirén S, Vilo S, Manner T, Scheinin M, Saari TI. Pharmacokinetics and sedative effects of intranasal dexmedetomidine in ambulatory pediatric patients. Anesth Analg. 2019 Jun 12. doi: 10.1213/ANE.0000000000004264. [Epub ahead of print]

IV Uusalo P, Lehtinen M, Löyttyniemi E, Manner T, Scheinin M, Saari TI. Premedication with intranasal dexmedetomidine decreases thiopental requirements in sedation of pediatric patients for magnetic resonance imaging: a register-based study. BMC Anesthesiol. 2019;19(1):22–27.

V Uusalo P, Jätinvuori H, Löyttyniemi E, Kosola J, Saari TI. Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia. J Arthroplasty. 2019; 34(4):686-692.

I INTRODUCTION

The most important reasons why many patients need sedation during perioperative care are pain management, patient comfort and patient and personnel safety. Sedation may also be needed when attempting various interventions, such as to facilitate the management of respiratory problems (Devlin 2008). Conventional sedative drug regimens in the intensive and perioperative care settings have primarily consisted of $GABA_A$ receptor modulators such as propofol, benzodiazepines and barbiturates (Devlin and Roberts 2011). Opioids are also widely used to treat pain and to facilitate procedures that require sedation. Both $GABA_A$ modulators and opioids carry a risk of respiratory depression and may predispose patients to respiratory complications as well as to increased morbidity and mortality. Furthermore, these agents are challenging to use for long-term sedation, because they may accumulate in an unpredictable manner (Kollef et al. 1998, Swart et al. 2006, Barr et al. 2001). α_2-Adrenoceptor agonists are now challenging the traditional sedative agents since they inhibit neuronal activity by a unique mechanism of action, evoking sedative and analgesic effects and centrally mediated sympatholysis. α_2-Adrenoceptor agonists are already in worldwide use as components of multimodal procedural and intensive care sedation and analgesia (Wujtewicz et al. 2003, Aantaa et al. 2015, Helander 2017).

Several α_2-adrenoceptor agonist drugs have been employed for patient sedation in the intensive care and perioperative care settings. Dexmedetomidine is the most selective and specific of the currently available α_2-adrenoceptor agonists. Compared to clonidine, another widely used α_2-adrenoceptor agonist, the α_2-/α_1-selectivity ratio of dexmedetomidine is approximately eight-fold (1600:1). Dexmedetomidine has been registered in approximately 70 countries for continuous intravenous infusion for sedation of intubated and mechanically ventilated adult patients in intensive care units (ICU). Additionally, dexmedetomidine also has approval for procedural sedation in some countries (Orion corp. 2018, Marko Hannula, Orion Pharma, e-mailed personal communication February 15th 2019).

Dexmedetomidine is often administered as a continuous intravenous infusion (Orion corp. 2018). In addition, many investigator-initiated clinical studies have reported on the extravascular administration of dexmedetomidine, with intramuscular injections and intranasal administration being the most extensively investigated; there is convincing evidence to support the intranasal use of dexmedetomidine. However, detailed pharmacokinetic information has been lacking on these delivery routes, and therefore further studies are warranted in order to ensure that extravascular administration of dexmedetomidine is both safe and practical. Any

delivery mode other than intravenous use of dexmedetomidine is currently considered off-label (Karaaslan et al. 2006, Iirola et al. 2011a)

There are several published case reports and uncontrolled studies (Soares et al. 2002, Kent et al. 2005) indicating that dexmedetomidine may provide benefits for patients in palliative care as it induces analgesia, sympatholysis and sedation with relatively little risk of respiratory depression. Intravenous administration of analgesic or sedative agents is often unsuitable for palliative care patients, and alternative administration routes are beneficial but before extravascular administration routes can become routine, there must be evidence from pharmacokinetic and pharmacodynamic studies that they are feasible.

No current sedative agent appears to be ideally suited for procedural sedation of pediatric patients. Although dexmedetomidine does not have regulatory approval for use in this population, it is quite commonly used for pediatric ICU sedation. Increasingly, many pediatric operation units use dexmedetomidine as premedication and as an anesthetic adjunct (Mason and Lerman 2011). Since developmental and physiological changes in children contribute to the age-related variation in drug disposition (Thakkar et al. 2017), clinical evaluations on the pharmacokinetic and pharmacodynamic properties of dexmedetomidine in pediatric patients are clearly warranted.

In the present series of studies, we characterized the pharmacokinetics and pharmacodynamics of subcutaneously and intranasally administered dexmedetomidine in healthy adult volunteers and in pediatric patients. We also examined whether intranasally administered dexmedetomidine would have anesthetic-sparing effects in pediatric patients undergoing ambulatory sedation and analgesic-sparing effects in adult patients undergoing hip arthroplasty under general anesthesia.

II REVIEW OF THE LITERATURE

2.1 Alpha-adrenoceptors

2.1.1 History and classification of adrenoceptors

Adrenoceptors are membrane-bound G-protein coupled receptors that are located on neurons and non-neuronal cell membranes throughout the body. Adrenoceptors bind and are activated by two endogenous catecholamines, adrenaline and noradrenaline, but are also targeted by many synthetic therapeutic agents (Maze and Regan 1991).

Adrenoceptors have been extensively investigated as they are mediators of many physiologically important effects e.g. the regulation of endocrine, neuronal, vascular and metabolic activities. Already in 1948, these receptors were divided into two main types, α- and β-adrenoceptors, based on the rank order of potency of various natural and synthetic catecholamines in different physiologic test preparations. At that time, α-adrenoceptors were considered to mediate the excitatory effects of catecholamines whereas β-adrenoceptors were considered to mediate inhibitory effects (Ahlquist et al. 1948).

In 1974, Langer et al. presented the concept that α_1-adrenoceptors were excitatory and mediated postsynaptic responses to catecholamines in target organs, whereas presynaptically located α_2-adrenoceptors evoked inhibitory effects by preventing the release of noradrenaline from nerve endings (Langer et al. 1974). Further studies, however, revealed that α-adrenoceptors could not be classified based on their anatomical locations alone, but instead a subdivision was devised according to the functions mediated by each type of receptor and their respective ligands (Berthelsen and Pettinger 1977).

In 1967, the β-adrenoceptors were divided into two subtypes, β_1 and β_2 (Lands et al. 1967), and during the 1980s, the research group of Lefkowitz and Kobilka managed to identify the gene that encodes the β_2-adrenoceptor. This research revealed that the receptor consisted of seven hydrophobic spiral strings that were each long enough to span the cell membrane – so-called α-helices (Dixon et al. 1986). Three decades later, Kobilka's research group was able to capture an image of the β_2-adrenoceptor at the very moment when it transferred the signal from the hormone on the outside of the cell to the G-protein inside the cell (Rasmussen et al. 2011). This research was honoured with the award of Nobel Prize in Chemistry in 2012 (Benovic 2012).

Advances made with molecular biological techniques and radioligand binding assays have helped to clarify the subtypes of adrenoceptors (Aantaa et al. 1995). In 1994, radioligand binding experiments revealed that there were four pharmacologically distinct subtypes of α_2-adrenoceptors, α_{2A}, α_{2B}, α_{2C} and α_{2D} (Bylund et al. 1994), but later studies revealed that human α_{2A}- and rat α_{2D}-adrenoceptors were encoded by splicing variants of the same α_{2A}-adrenoceptor gene. Today, it is known that the adrenoceptor family includes nine different gene products in mammals: three β- (β_1, β_2 and β_3), three α_1- (α_{1A}, α_{1B}, α_{1D}) and three α_2-adrenoceptors (α_{2A}, α_{2B} and α_{2C}) (Cotecchia et al. 2010) (Figure 1). The α_1- and α_2-adrenoceptor subtypes are located in various organs, including heart, blood vessels, brain, kidney, liver and spleen. In most tissues, activation of α_1-adrenoceptors triggers polyphosphoinositide hydrolysis catalyzed by phospolipase C via pertussis toxin-insensitive G-proteins (Graham et al. 1996). The most important therapeutic effect of α_1-adrenoceptor activation is vasoconstriction and increased blood pressure. β-Adrenoceptor subtypes mediate the actions of catecholamines and many therapeutic agents, via adenylate cyclase stimulation through heterotrimeric G_s-proteins, by increasing intracellular concentrations of cAMP and by regulating L-type calcium channels in the cell membrane, leading to the characteristic physiological responses such as smooth muscle relaxation and bronchodilation (Yu et al. 1993).

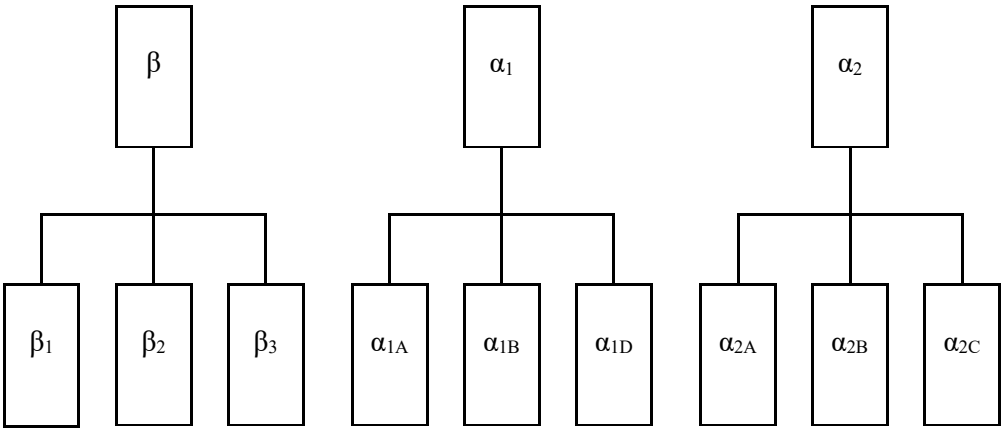

Figure 1. The adrenoceptor family.

2.1.2 α_2-Adrenoceptors

The best known function of α_2-adrenoceptors is to mediate the physiological feedback inhibition of noradrenaline release from nerve endings. α_2-Adrenoceptors, located on presynaptic sympathetic neuronal membranes, inhibit the release of neurotransmitters from vesicles containing noradrenaline and several co-transmitters, including neuropeptide Y and ATP; these receptors are called autoreceptors (Burnstock et al. 1990). Presynaptic release-modulating α_2-adrenoceptors that are located on cells releasing other neurotransmitters than noradrenaline are often called heteroreceptors (Starke et al. 2001).

All three α_2-adrenoceptor subtypes share similar signaling properties (Limbird et al. 1988). The most obvious functionally important differences between the three α_2-adrenoceptor subtypes are their different cellular and tissue localizations that result in different physiological functions and pharmacological activity. All α_2-adrenoceptor subtypes are able to inhibit endogenous transmitter release from postganglionic sympathetic neurons (Trendelenburg et al. 2003), but differ in their pharmacological properties, sensitivity to phosphorylation, desensitization and internalization (Philipp et al. 2002).

Specific physiological functions of α_2-adrenoceptor subtypes have been identified in the peripheral nervous system, in the central nervous system, and in a variety of organs and cell types, including the liver, pancreas, kidney, blood platelets and eyes (Szabo et al. 1989). α_{2A}-Adrenoceptors are expressed widely in the central nervous system, especially in noradrenergic cell body regions such as the locus coeruleus in the brain stem (Scheinin et al. 1994, MacDonald and Scheinin 1995). α_{2A}-Adrenoceptors have also been found in the prefrontal cortex, perhaps explaining why α_{2A}-adrenoceptor agonists may be beneficial in the treatment of attention deficit and hyperactivity disorder (Ma et al. 2015). Peripheral locations where α_{2A}-adrenoceptors are the dominant subtype are human blood platelets, aorta and spleen. α_{2B} -Adrenoceptors have been found to be sparsely expressed in the central nervous system, although with relatively most abundant expression in the thalamus. In the periphery, α_{2B}-adrenoceptors are present in heart and liver (MacDonald and Scheinin 1995, Wang et al. 2002, Gyires et al. 2009). The α_{2C}-subtype is the dominant α_2-adrenoceptor subtype in the spinal cord, although the spinal cord appears to express all three subtypes. Examples of the tissue localizations and physiological functions of the three α_2-adrenoceptor subtypes are summarized in Table 1.

Table 1. Examples of the tissue localizations, physiological functions and pharmacological responses of α_2-adrenoceptor subtypes.

Receptor	Localizations	Physiological functions and responses
α_{2A}	Locus coeruleus, Pontine nuclei, Midbrain, Cerebral cortex, Amygdaloid complex, Hypothalamus, Spinal cord, Platelets, Aorta, Spleen, Kidney, Vascular smooth muscle, Endothelium	Presynaptic inhibition of neurotransmitter release, Hypotension, Bradycardia, Sedation, Anesthetic sparing effect, Hypothermia, Antinociception, Inhibition of gastric emptying, Vascular smooth muscle contraction, Platelet aggregation
α_{2B}	Thalamus, Lungs, Vascular smooth muscle, Kidneys, Uterus	Vascular smooth muscle contraction, Hypertension, Bradycardia, Salt-induced hypertension
α_{2C}	Cerebral cortex, Basal ganglia, Hippocampus, Spinal cord, Vascular smooth muscle, Kidneys, Olfactory system	Presynaptic inhibition of neurotransmitter release, Hypothermia, Antinociception, Vascular smooth muscle contraction

Modified from Blaxall et al. 1994, MacDonald and Scheinin 1995, Hunter et al. 1997, Trendelenburg et al. 2003, Gyires et al. 2009 and Gilsbach et al. 2011

The α_2-adrenoceptors are coupled to pertussis-toxin-sensitive $G_{\alpha 0}$-proteins that regulate ion channels and $G_{\alpha i}$-proteins that mediate inhibition of adenylyl cyclases (Freissmuth et al. 1989). When an agonist binds to a G-protein coupled α_2-adrenoceptor, the receptor structure becomes slightly altered, leading to a conformational change in the associated α-subunit of the G-protein. Activation of $G_{\alpha i}$-protein inhibits intracellular adenylyl cyclase enzymes, which in turn leads to reduced formation of the second messenger, cAMP. This regulates many important cellular functions by controlling the phosphorylation state of regulatory proteins via a cAMP-dependent protein kinase, protein kinase A (Birnbaumer et al. 1990). Activation of α_{2A}-adrenoceptors evokes centrally mediated inhibition of the peripheral sympathetic nervous system, which can be seen as diminished catecholamine levels in plasma. The ensuing attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery is often beneficial (Gertler et al. 2001).

2.1.3 α_2-Adrenoceptor agonists

In 1960, the German pharmaceutical company Boehringer-Ingelheim was developing a novel drug to be marketed as a nasal decongestant. When used to treat the symptoms of common cold in one of the laboratory staff members, a drop of a 0.3% solution of this 2,6-dichloro-substituted imidazole compound (clonidine) was administered into both nostrils. Unexpectedly, the subject fell asleep and developed low blood pressure, marked bradycardia and dryness of the mouth. Thereafter, this

drug molecule's decongestant properties were considered to be far less interesting than its potent anti-hypertensive activity, and as a result, clonidine was introduced in 1966 for the treatment of hypertension (Stähle et al. 2000).

Later, many therapeutic indications have emerged for α_2-adrenoceptor agonist drugs. The imidazole derivatives xylazine, detomidine and medetomidine have been used in veterinary sedation for almost 40 years (Tranquilli et al. 1992). Off-label use of clonidine has extended to sedation and analgesia of critically ill patients and to its use as an anesthetic and intrathecal adjunct (Wang et al. 2017, Crespo et al. 2017). In the year 2000, clonidine received approval from the FDA for the treatment of Attention Deficit Hyperactivity Disorder in children aged 6-17 years (Sallee et al. 2013). Clonidine has also been used in the treatment of opioid and alcohol withdrawal symptoms (Gowing et al. 2016). Apraclonidine and brimonidine are used as eye drops to treat glaucoma (Arthur et al. 2011). Tizanidine has been found to be equally effective but better tolerated than some other anti-spasticity drugs such as baclofen and diazepam in the treatment of neurological patients (Kamen et al. 2008). Rilmenidine and moxonidine are used as antihypertensives: these compounds have been postulated to exert their pharmacological effects by activating imidazole receptors in addition to being α_2-adrenoceptor agonists (Khan et al. 1999).

2.1.4 α_2-Adrenoceptor antagonists

In veterinary medicine, the α_2-adrenoceptor agonists xylazine, detomidine, medetomidine and dexmedetomidine are commonly used for sedation and analgesia, and atipamezole, an α_2-adrenoceptor antagonist, has been used to reverse their effects when sedation is no longer needed (Aantaa et al. 1995). In addition, Karhuvaara et al (1991) administered atipamezole intravenously to human volunteers in order to reverse the effects of dexmedetomidine. Atipamezole, the most selective α_2-adrenoceptor antagonist then available, was able to reverse the sedation and hypotension evoked by dexmedetomidine (Karhuvaara et al. 1991).

2.2 Dexmedetomidine

2.2.1 Molecule and history

Dexmedetomidine (4-[(1S)-1-(2,3-dimethylphenyl)-ethyl]-1H-imidazole), an imidazole compound (Figure 2), is the pharmacologically active dextroisomer of medetomidine, with the molecular formula $C_{13}H_{16}N_2$. Dexmedetomidine has a pKa of 7.1 and a logP of 2.9. Its hydrochloride salt is freely soluble in water. The

molecular weight of dexmedetomidine hydrochloride is 236.7 g/mol. It is a highly selective α_2-adrenoceptor agonist with a relatively high selectivity ratio for α_2/α_1-adrenoceptors (1620:1 as compared to 220:1 for clonidine) (Orion corp. 2018). The lipid solubility of dexmedetomidine is 3.5 times higher than that of clonidine, which enables it to diffuse more easily into the central nervous system. Its high lipophilicity and relatively rapid elimination mean that the drug has an excellent spectrum of effects i.e. efficacy, a good safety profile with a very rapid onset of action and a short duration of clinical effects (Grosu et al. 2010).

Dexmedetomidine was originally developed by the Finnish pharmaceutical research and development company, Farmos Pharma. In the 1980s, Farmos Pharma was conducting human pharmacological studies with racemic medetomidine. Since the drug authorities were already at that time favoring the use of active enantiomers, dexmedetomidine was developed and administered for the first time to healthy human volunteers in 1987. The aim was to develop a drug that could be used as anesthesia premedication before medical procedures (Kallio et al. 1989). The sedative, sympatholytic and hemodynamic effects of dexmedetomidine were documented already in the first clinical studies. At the beginning of the 1990s, dexmedetomidine was administered intramuscularly to hundreds of patients (Scheinin et al. 1992, Scheinin et al. 1993, Dyck et al. 1993a). These studies have later been considered as phase II-III studies. At the same time, many investigators became interested in the possible cardioprotective effects of dexmedetomidine (Bloor et al. 1992, Dyck et al. 1993b). The sympatholytic effect of dexmedetomidine was thought to stabilize intraoperative changes in blood pressure and HR, thus they could help to prevent cardiac ischemia. Perioperative infusions of dexmedetomidine were found to be beneficial in the perioperative hemodynamic management of patients undergoing vascular surgery (Talke et al. 1995).

Dexmedetomidine was introduced into clinical practice in the United States in 1999 and was at that time approved by the FDA only for short-term (<24 hours) sedation of mechanically ventilated adult patients in the ICU. At the same time, the EMA was not willing to approve dexmedetomidine since all controlled clinical trials had been conducted with only placebo as comparator. Based on two extensive phase III clinical trials, PRODEX and MIDEX, a product called Dexdor® received European marketing authorisation in September 2011 (Kallio and Aantaa 2012). The PRODEX and MIDEX trials showed that dexmedetomidine was successful in reducing the duration of mechanical ventilation compared with midazolam, but tended not to be inferior to the standard sedatives, propofol and midazolam, in maintaining light to moderate sedation (Jakob et al. 2012). In 2018, dexmedetomidine received an indication for sedation of non-intubated adult patients prior to and/or during

diagnostic or surgical procedures requiring sedation (i.e. procedural/awake sedation) in Finland and many other countries (Orion corp. 2018). Several published reports exist regarding off-label use of dexmedetomidine as an adjunctive anesthetic and analgesic during general anesthesia (Piao et al. 2014, Wu et al. 2016) and in treating alcohol and opioid withdrawal symptoms (Wong et al. 2015, Oschman et al. 2011). Dexmedetomidine has also been described as a useful and safe adjunct in many other clinical applications, such as treating glaucoma, reducing sympathetic overactivity, alleviating withdrawal symptoms or pain in the terminal stages of life (Gilsbach and Hein 2012, Jackson et al. 2006). Off-label use of dexmedetomidine in the pediatric patient population is very common and this will be discussed in Chapter 2.5.

2.2.2 Pharmacokinetics of dexmedetomidine

After intravenous administration to healthy human volunteers, dexmedetomidine has been shown to have a distribution half-life of approximately 6 min (Karol and Maze 2000). One-, two- and three-compartment disposition models have been used to describe the pharmacokinetics of dexmedetomidine (Talke et al. 1997, Venn et al. 2002, Lin et al. 2011, Iirola et al. 2012, Välitalo et al. 2013).

In plasma, dexmedetomidine is bound to albumin and α_1-acid-glycoprotein. The average extent of protein binding is 94%; some displacement from plasma protein binding sites has been reported by fentanyl, ketorolac, theophylline, digoxin and lidocaine, all of which are drugs commonly used during anesthesia and in the ICU (Gertler et al. 2001). In healthy volunteers, the apparent volume of distribution has been reported to be approximately 1.31–2.46 L/kg at steady state. In the critically ill, these values are far more variable, with mean volumes of distribution ranging from 109 to 223 L (Weerink et al. 2017).

Although dexmedetomidine has only approval for intravenous administration, its bioavailability has been investigated after administration by various extravascular routes i.e. intramuscular, transdermal, buccal, intranasal and peroral administration (Scheinin et al. 1992, Dyck et al. 1993a, Kivistö et al. 1994, Anttila et al. 2003, Iirola et al. 2011a). The pharmacokinetic properties of extravascularly administered dexmedetomidine are summarized in Table 2, and the various extravascular administration routes of dexmedetomidine are discussed more comprehensively in Chapter 2.6.

The major metabolic pathways of dexmedetomidine are direct N-glucuronidation to form inactive conjugated metabolites, oxidation and hydroxylation, primarily mediated by CYP2A6, and N-methylation (Figure 2). The most abundant circulating

metabolites of dexmedetomidine are two isomeric N-glucuronides (G-Dex-1 and G-Dex-2) (41%). Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation (21%). Cytochrome P-450 enzymes catalyse the formation of two minor circulating metabolites, H-3 is produced by oxidation of the imidazole ring (11%) and 3-hydroxymethyl dexmedetomidine results from the hydroxylation at the drug's 3-methyl group (Ji et al. 2004, Orion Corp. 2018). There is also some data suggesting that the formation of the oxidised metabolites is mediated by several CYP isoforms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity (Karol and Maze 2000).

Dexmedetomidine is mainly eliminated through biotransformation in the liver and less than 1% of a dose is excreted unchanged in urine and faeces. After intravenous infusion of 2 µg/kg of radioactive [^{3}H]-dexmedetomidine, 95% of the total radioactivity was found in the urine and only 4% in the faeces (Karol and Maze 2000). A hepatic extraction ratio of 0.7 has been reported (Dutta et al. 2000). In healthy volunteers, the average terminal half-life has been reported to be 2.0-3.1 h and CL 0.5-0.8 l/min (Venn et al. 2002, Anttila et al. 2003, Iirola et al. 2011).

Dexmedetomidine has major effects on cardiovascular function, potentially causing bradycardia, hypotension or transient hypertension that may impact on its own pharmacokinetics. At high plasma concentrations, marked vasoconstriction occurs, which may well reduce the drug's volume of distribution. Dutta et al (2000) used a computer-controlled infusion protocol and investigated the effect of cardiac output on the elimination of dexmedetomidine. Increasing plasma concentrations of dexmedetomidine decreased cardiac output, resulting in a corresponding decrease in drug elimination CL by ≤ 12%, but the decrease in dexmedetomidine CL was not regarded as clinically relevant in the therapeutic concentration range (Dutta et al. 2000). Dexmedetomidine decreases hepatic blood flow, which may have an impact on the CL of some drugs, at least in theory.

Table 2. Previous pharmacokinetic human studies of extravascular administration of dexmedetomidine.

Author and year	Scheinin 1992	Dyck 1993a	Kivistö 1994	Anttila 2003	Iirola 2011a	Li 2018	Miller 2018
Administration route	IM	IM, IV	TD, IV	PO, buccal, IM, IV	IN, IV	IN, IV	IN, IV
Subjects	Male volunteers	Male volunteers	Healthy males	Healthy males	Male volunteers	Healthy adults	Pediatric patients
No of subjects	6	10	9	12	6	8	12
Dose	0.5, 1.0, 1.5 ug/kg	2.0 ug/kg	625 ug/12 h	2.0 ug/kg	84 ug	1.0 ug/kg	1.0-2.0 ug/kg
T_{max} (min)*	96-102	13	N/A	72, 114 and 132	38	60	46
C_{max} (ng/ml)*	0.14, 0.26, 0.34	0.80	N/A	0.11, 0.29 and 0.51	0.34	0.25 - 0.28	0.18 - 0.32
F*	N/A	73%	51%	16%, 82%, 104%	65%	41%	82%

* Corresponding parameters after extravascular administration reported, IM; intramuscular, IN; intranasal, IV; intravenous, PO; per oral, TD; transdermal

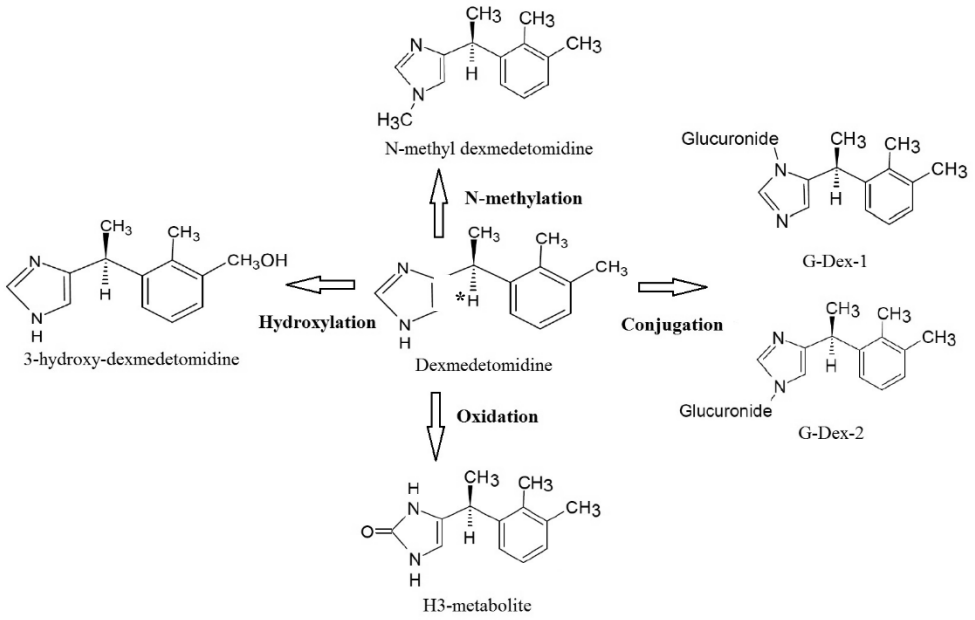

Figure 2. The structural formula of dexmedetomidine and the first steps in its proposed metabolic scheme.

*stereocentre

2.2.3 Pharmacokinetics in special populations

Age, gender and race

In a phase I pre-registration study conducted by Abbott Laboratories, no differences were found in the pharmacokinetics of dexmedetomidine in healthy volunteers between groups of young (18–40 years), middle-aged (41–65 years) and elderly (>65 years) subjects (Hospira Inc. 2016). In critically ill patients, age was found to be a covariate for dexmedetomidine pharmacokinetics, but results on this issue have been inconsistent and no definitive conclusions about the findings can be made (Iirola 2012, Lee et al. 2012, Kuang et al. 2016). Elimination of dexmedetomidine in children (1 months to 17 years) appears similar to that in adults, but in newborn infants (under 1 month), it may be slower (Hospira Inc. 2016). No major pharmacokinetic differences have been observed between the sexes. There is only little evidence of ethnic differences in the metabolism of dexmedetomidine (Kurnik et al. 2011).

Hepatic and renal impairment

Dexmedetomidine is mainly metabolized by the liver, and its plasma protein binding may be decreased in subjects with hepatic impairment as compared to healthy subjects. In a pre-registration study conducted by Abbott Laboratories, mean CL estimates in patients with mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, or C) were 74, 64, and 53% of those found in healthy subjects. The mean elimination half-life of dexmedetomidine in healthy subjects was 2.5 h and it was prolonged to 3.9, 5.4, and 7.4 h in patients with mild, moderate, and severe hepatic impairment, respectively (Weerink et al. 2017).

Rolle et al (2018) investigated the pharmacokinetics of intraoperatively administered dexmedetomidine in forty patients undergoing abdominal laparoscopy. Hepatic blood flow, liver histopathology, liver enzymes, and gene expression of some metabolizing enzymes (UGT2B10 and µgT1A4) were tested as covariates of dexmedetomidine metabolic CL; liver blood flow was found to be a covariate for dexmedetomidine CL (Rolle et al. 2018).

Hepatic impairment and some other chronic illnesses may reduce albumin levels in plasma and this may exert significant effects on dexmedetomidine's pharmacokinetics (Iirola et al. 2012, Lee et al. 2012, Välitalo et al. 2015). For example, an increased unbound fraction of dexmedetomidine in plasma may lead to prolonged effects as compared to healthy volunteers.

The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance < 30 ml/min) have not been found to be different relative to healthy subjects. When the pharmacokinetics of dexmedetomidine were compared in renally impaired patients and healthy volunteers, no differences were found in the volume of distribution or in the elimination CL (De Wolf et al. 2001, Zhong et al. 2018).

Critically ill patients

Only limited information is available on the pharmacokinetics of long-term administration of dexmedetomidine in critically ill patients, and extensive inter-individual variability has been described in an ICU population. In two studies assessing the population pharmacokinetics of dexmedetomidine infusions in critically ill ICU patients, age and body weight were found to be negatively associated with dexmedetomidine's CL (Iirola et al. 2012, Välitalo et al. 2015).

Obese patients

Many studies have found that body weight has an influence on the pharmacokinetics of dexmedetomidine (Välitalo et al. 2013, Hannivoort et al. 2015, Kuang et al. 2016). Cortinez et al (2015) compared the pharmacokinetics of intraoperatively administered dexmedetomidine in obese (BMI >35 kg/m^2) and non-obese (BMI 18.5–30 kg/m^2) patients undergoing laparoscopic surgery. Patients received a loading dose of 0.5 µg/kg of dexmedetomidine followed by a constant-rate infusion of 0.25 to 0.5 µg/kg/h. A two-compartment pharmacokinetic model was employed, and fat free mass was found to the best covariate of dexmedetomidine's pharmacokinetics (Cortinez et al. 2015). Based on reported pharmacokinetic studies, it appears that the body weight-adjusted dosing scheme that is currently applied is only reliable for non-obese patients; for obese patients, dosing should be based on fat-free mass. It has been claimed that if total body weight is used for weight-adjusted dosing of dexmedetomidine, it may lead to overdosing of obese subjects (Weerink et al. 2017).

Pediatric patients

There is rather limited information on the pharmacokinetics of dexmedetomidine in pediatric patients. In small children aged 2-20 months or 2-6 years, body weight-adjusted plasma CL appeared to be larger (1.2 and 1.0 l/h/kg, respectively) than in adults (0.5-0.6 l/h/kg), but older children had an average CL that was comparable to adults (0.8 l/h/kg) (Potts et al. 2009, Hannivoort et al. 2015). In neonates aged < 2 months, the plasma CL may be lower due to hepatic immaturity (Su et al. 2016). The elimination half-life of dexmedetomidine appears similar in children and in adults (Petroz et al. 2006, Diaz et al. 2007, Vilo et al. 2008).

The pharmacokinetics of dexmedetomidine has been studied during more prolonged (45 - 223 h) infusions in critically ill children. Bayesian population modeling was employed to assess the drug concentrations measured during and after the infusions. It was found that the volume of distribution was increased 1.5-fold and clearance was increased 1.3-fold after termination of the infusion, once the concentration of dexmedetomidine had decreased to a level of approximately 1 ng/ml (Wiczling et al. 2015).

When the pharmacokinetics of intravenous dexmedetomidine infusions was studied in infants with postmenstrual age from 33 to 61 weeks, a younger postmenstrual age was a significant predictor of lower CL. For infants with postmenstrual age of 33 to 61 weeks and body weight of 2 to 6 kg, the estimated CL and volume of distribution were 0.87 to 2.65 l/h/kg and 1.5 l/kg, respectively (Greenberg et al. 2017).

2.2.4 Pharmacokinetic interactions of dexmedetomidine

Dexmedetomidine undergoes extensive biotransformation in the liver, this being partly mediated by cytochrome P450 enzymes. In vitro, dexmedetomidine has been found to inhibit some CYP enzymes (including CYP2B6) and to induce the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4. There is potential for interaction between dexmedetomidine and substrates which undergo extensive metabolism by CYP2B6 (e.g. bupropion, artemisinin, pethidine, methadone) (Orion corp. 2018). Flexman et al. found that two enzyme-inducing anticonvulsant drugs, phenytoin and carbamazepine, increased the elimination clearance of dexmedetomidine on average by 43% (range, 10-100%) (Flexman et al. 2014).

2.3 Pharmacodynamics of dexmedetomidine

2.3.1 Sedative, amnestic and anesthetic sparing effect

The α_{2A}-adrenoceptor subtype has been shown to be the primary mediator of the sedative properties of α_2-adrenoceptor agonists (Scheinin et al. 1994, Azure et al. 2010). Dexmedetomidine causes fatigue by activating α_2-adrenoceptors in the main noradrenergic cell body region of the brain, the locus coeruleus, which expresses α_{2A}-adrenoceptors at a very high density (Wang et al. 1996). It affects the physiological state of vigilance by modulating the activity of GABA-ergic neurons of the pre-optic nucleus in the rostral hypothalamus as well as the activity of the descending medullospinal noradrenergic pathways. Hyperpolarization of noradrenergic neurons in the locus coeruleus suppresses noradrenaline release, leading to increased GABA and galanine activity in the tuberomamillary nucleus, which inhibits histamine secretion in cortical and subcortical projections (Figure 3) (Nelson et al. 2003). This results in hyperpolarization of spontaneously activated cells; this phenomenon is reflected as a naturally-occurring non-REM sleep pattern in electroencephalography (EEG) recordings (Guo et al. 1996, Huupponen et al. 2008).

The light level of sedation, good patient co-operability and many of the additional properties associated with the drug, such as analgesia, make dexmedetomidine an almost ideal sedative agent to be used in the ICU setting. Memory was preserved in healthy volunteers receiving dexmedetomidine with low target plasma concentrations (up to 0.7 ng/mL) of dexmedetomidine (Ebert et al. 2000), but some other studies have shown that dexmedetomidine may exert some amnestic effects (Hall et al. 2000, Venn et al. 2002).

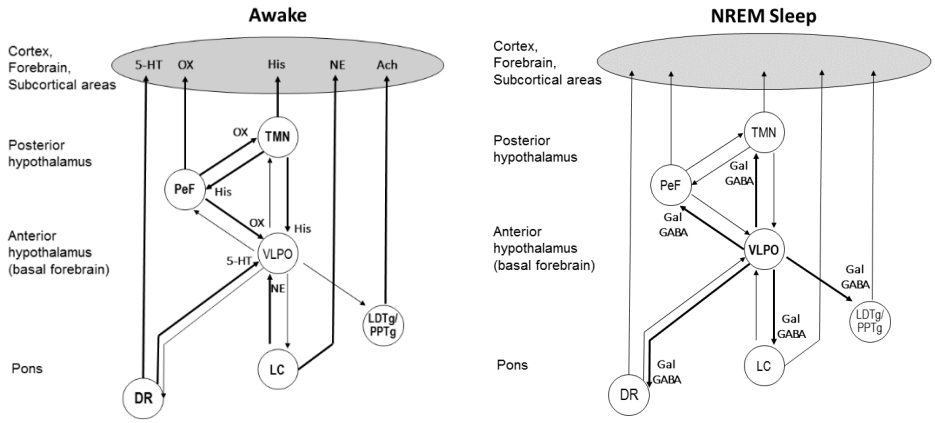

Figure 3. Neural mechanisms of α_2-adrenoceptor agonist-induced sedation. Wakefulness is promoted by the release of the arousal-promoting monoamine neurotransmitters, noradrenaline (NE), serotonin (5-HT), and histamine (His), from the locus coeruleus (LC), dorsal raphe nucleus (DR), and tuberomammillary nucleus (TMN), respectively, as well as acetylcholine (ACh) from the pedunculopontine and laterodorsal tegmental nuclei (PPTg and LDTg) and orexin (OX) from the perifornical area (PeF) into the cortex, forebrain, and subcortical areas. Conversely, during the deeper stages of non-REM sleep, the activity is reversed by the inhibitory action of GABA and galanin (Gal) released from the ventrolateral pre-optic nucleus (VLPO). Modified from Sanders and Maze, 2007.

Clonidine was reported to reduce the minimal alveolar concentrations of inhalational anesthetics when used as an anesthetic adjunct (Inomata 2000). Similarly, dexmedetomidine lessened the need for intraoperative isoflurane (Aantaa et al. 1997) in adults and sevoflurane in pediatric patients (Savla et al. 2014). Intravenous dexmedetomidine infusions decreased the propofol concentrations required for sedation and suppression of motor responses (Dutta et al. 2001). The distribution of thiopental was reduced after dexmedetomidine administration; this was thought to be related to the decline in cardiac output and changes in regional blood flow. Similarly, dexmedetomidine reduced thiopental requirements to achieve EEG burst suppression (Bührer et al. 1994).

2.3.2 Analgesic and opioid sparing effects

The antinociceptive effects of α_2-adrenoceptor agonists and the neuronal circuits involved have been extensively investigated. Analgesic effects of α_2-adrenoceptor agonists are thought to occur both in the spinal cord and in the brain. In animal models, clonidine has been found to reduce the excitation caused by nociceptive stimuli in the dorsal root ganglia that are involved in the sensation of pain (Yagi et al. 1998, Wolff et al. 2007). It has been postulated that the activation α_{2C} - and α_{2A}-adrenoceptors located in the dorsal horn of the spinal cord of rats by

dexmedetomidine suppressed pain transmission by reducing the release of the nociceptive transmitters, substance P and glutamate, and by hyperpolarization of interneurons (Ishii et al. 2008). In addition, clonidine has been found to prevent effectively the activation of hyperpolarization-activated cyclic nucleotide–gated channels in various types of nerve cells, such as neurons of the prefrontal cerebral cortex (Carr et al. 2007) and in dopaminergic nerve cells in the ventral tegmentum of the ventral forebrain (Inyushin et al. 2010).

Animal studies have shown that α_2-adrenoceptor agonists enhance opioid analgesic effects by prolonging the duration of analgesia and to a certain extent, by reducing the need for opioids to achieve analgesia (Meert et al. 1994). Opioids and dexmedetomidine have been found to display so-called isobolographic synergistic interactions. Dexmedetomidine has been reported to reduce the need for morphine and to lessen the development of chronic or neuropathic pain (Maze and Tranquili 1991; Ossipov et al. 1989). In addition, dexmedetomidine has been demonstrated to exert neuroprotective effects in some animal models. There was a significant decrease in the extent of direct brain damage in the group of mice that received prophylactic dexmedetomidine before brain injury; this effect seemed to be mediated through the α_{2A}-adrenoceptor subtype (Kingery et al. 2000). In another animal model, the combination of dexmedetomidine and lidocaine was found to reduce the emergence of ischemic brain injury (Goyagi et al. 2009).

The analgesic effects of dexmedetomidine and clonidine have been widely investigated in humans. Clonidine has long been used as an adjuvant in neuraxial blockade, especially when the combination of an opioid and a local anesthetic does not produce adequate analgesia (Allen et al. 2018). Likewise, dexmedetomidine is known to decrease the need for local anesthetics when administered as an adjuvant into the intrathecal or epidural space. When 1 or 2 μg/kg of dexmedetomidine was administered to augment sacral block by bupivacaine in pediatric patients aged from 1 to 6 years, the need for additional analgesics was significantly reduced in both dexmedetomidine groups as compared to patients receiving only bupivacaine (Al-Zaben et al. 2015). In another study, sixty pediatric patients undergoing lower abdominal surgery received a single dose of epidural ropivacaine, with or without dexmedetomidine. In the dexmedetomidine group, the postoperative pain as well as the postoperative need for analgesics were significantly lessened for up to 18 hours after surgery (Kamal et al. 2016).

Intravenous administration of dexmedetomidine has been found to decrease the need for postoperative opioids in patients undergoing surgery. In a double blind randomized controlled trial, patients undergoing total knee arthroplasty received

spinal anesthesia, and half of the patients were sedated with intravenous dexmedetomidine (approximately 1 μg/kg) in the procedure. Postoperative opioid consumption was significantly less in patients receiving dexmedetomidine for sedation. There was also a delay in the time to the first analgesic request (Chan et al. 2016). In healthy volunteers, intravenous bolus doses of dexmedetomidine (0.25-1.0 μg/kg) were found to be equally efficacious as intravenous fentanyl (2.0 μg/kg) in the treatment of ischemic limb pain (Jaakola et al. 1991).

Preoperatively administered dexmedetomidine has been shown to reduce intraoperative and postoperative opioid consumption in patients undergoing surgery (Lawrence et al. 1997, Scheinin et al. 1993). Furthermore, systemically administered dexmedetomidine was reported to prolong the effect of intrathecal (Kaya et al. 2010) and plexus anesthesia (Rutkowska et al. 2009). In addition to its analgesic effect, when used as an intraoperative adjunct, dexmedetomidine was claimed to alleviate postoperative anxiety and to inhibit agitation in children (Patel et al. 2010).

2.3.3 Effects on gastrointestinal functions

When administered to laboratory animals and healthy volunteers, dexmedetomidine has been found to inhibit gastric emptying and gastrointestinal transit (Asai et al. 1997, Iirola et al. 2011b). When healthy volunteers received 1 μg/kg of dexmedetomidine infused over 20 min followed by 0.7 μg/kg infusion for 190 min, it was found that dexmedetomidine quite markedly inhibited gastric emptying and prolonged gastrointestinal transit times. The effects were clearly more pronounced than those of the active comparator used in this trial, morphine (dosed 0.1 μg/kg intravenously) (Iirola et al. 2011b).

On the other hand, dexmedetomidine has opioid sparing effects, which may help to reduce the constipation, nausea and vomiting caused by opioid drugs (Gertler et al. 2001, Blaudszun et al. 2012). In some recent studies, dexmedetomidine has actually been shown to improve postoperative gastrointestinal motility in patients undergoing laparoscopic colonic resection (Chen et al. 2016, Wan et al. 2018). The clinical significance of the impact of dexmedetomidine on gastrointestinal functions is thus uncertain and may depend on individual patient characteristics.

2.3.4 Effects on hemodynamics

The two most evident effects of α_2-adrenoceptor agonists on hemodynamics are bradycardia and hypotension. Clonidine, moxonidine and rilmenidine have been widely used for the treatment of essential hypertension. Upon intravenous

administration, the hemodynamic effects of dexmedetomidine and other α_2-adrenoceptor agonists have, however, been found to be biphasic. The sympatholytic effects induced by these drugs are mediated via the central nervous system, whereas activation of vascular α_2-adrenoceptors mediates vasoconstriction and hypertensive effects (Figure 4).

The hemodynamic effects of dexmedetomidine have been studied with various target concentrations in healthy volunteers. With high dexmedetomidine concentrations (i.e. > 3 ng/ml), HR decreased by up to 29% from baseline. Reductions in HR were seen until the plasma dexmedetomidine concentration was 3.2–5.1 ng/mL, after which a plateau was reached (Ebert et al. 2000).

Talke et al. (2003) investigated dexmedetomidine-induced peripheral vasoconstriction in healthy volunteers. They found that low concentrations of dexmedetomidine in plasma induced vasodilation by reducing sympathetic tone, whereas high dexmedetomidine concentrations constricted blood vessels. The peripheral vasoconstrictive effects of low dexmedetomidine concentrations were more evident after pharmacological sympathectomy, i.e. brachial plexus block with a local anesthetic (Talke et al. 2003).

The effects of dexmedetomidine on myocardial perfusion and cardiac function were assessed with positron emission tomography and transthoracic echocardiography. It was found that therapeutic plasma concentrations of dexmedetomidine clearly reduced myocardial blood flow, but plasma concentrations that significantly exceeded the recommended therapeutic level did not further attenuate myocardial perfusion nor did they induce any evident mismatch between cardiac oxygen demand and supply (Snapir et al. 2006).

It has been stated that special caution should be exercised when treating patients with unstable hemodynamics, patients with bradycardia or atrioventricular block or patients receiving digoxin (Mason et al. 2010). Dexmedetomidine has been listed as a drug that may impair cardiac repolarization and prolong the QT interval in the ECG, although there are also studies suggesting that dexmedetomidine may actually shorten corrected QT interval (QTc) (Görges et al. 2015, Kako et al. 2015).

In early animal studies, dexmedetomidine was found to reduce cerebral blood flow with no effect on the cerebral metabolic rate of oxygen, which raised concerns that the decreased blood flow might be inadequate for cerebral metabolic needs (Karlsson et al. 1990, Zornow et al. 1990). Farag et al (2017) compared regional brain oxygenation when patients were sedated with dexmedetomidine or propofol and observed that cerebral blood flow velocity was similarly preserved in both groups.

A recent study compared the effects of dexmedetomidine on the regional cerebral metabolic rate of glucose with three commonly used anesthetic drugs at equi-sedative doses. Compared to propofol, sevoflurane and ketamine, the regional cerebral metabolic rate of glucose was lowest in the dexmedetomidine group (Laaksonen et al. 2018). These recent findings have alleviated concerns about dexmedetomidine-induced vasoconstriction and cerebral ischaemia.

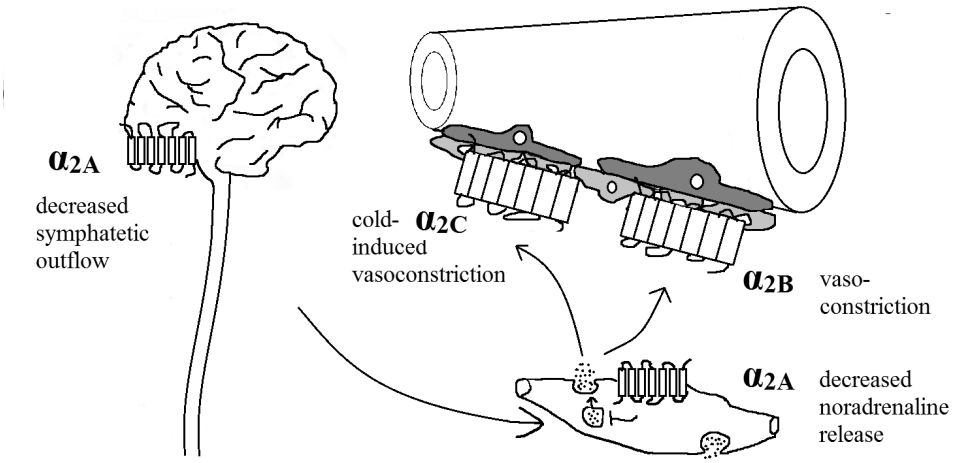

Figure 4. Integrative regulation of blood pressure by different α_2-adrenoceptor subtypes. Modified from Philipp et al. 2002.

2.3.5 Effects on respiration

Respiratory depression is a well known and common side effect of many anesthetics and sedatives. Dexmedetomidine has been widely considered to be a sedative that does not impair respiration. The effect of dexmedetomidine infusion on respiration has been studied in spontaneously breathing volunteers. Dexmedetomidine at concentrations producing significant sedation reduced minute ventilation, but did not affect arterial oxygenation, arterial pH, or the slope of the carbon dioxide ventilatory response curve (Ebert et al. 2000).

The effects of placebo, midazolam, propofol and dexmedetomidine on respiration have been compared in rabbits that had been anesthetized with sevoflurane. The apneic carbon dioxide thresholds of propofol and midazolam were larger than those of dexmedetomidine and placebo. The carbon dioxide sensitivity of the animals was somewhat reduced by dexmedetomidine as compared to placebo (Chang et al. 2009).

When dexmedetomidine was compared to propofol and midazolam in the sedation of ICU patients, it was found that dexmedetomidine was not inferior to midazolam and propofol in maintaining light to moderate sedation. Moreover, dexmedetomidine reduced the duration of mechanical ventilation in comparison with midazolam and improved the patients' ability to communicate about pain when compared with midazolam and propofol (Jakob et al. 2012).

A recent study demonstrated that dexmedetomidine-induced sedation reduced ventilatory responses to hypoxia and hypercapnia to a similar extent as sedation with propofol. However, in that study, hypoxia was induced by lowering the inspired oxygen fraction (Lodenius et al. 2017). In an RCT of patients with obstructive sleep apnea, patients sedated with dexmedetomidine maintained upper airway patency better than patients sedated with propofol (Shin et al. 2018); nonetheless but it does seem that dexmedetomidine should be used with caution in patients with obstructive sleep apnea.

Compared with other sedative agents, dexmedetomidine appears to be relatively safe with regard to respiration. However, dexmedetomidine is often administered concomitantly with other sedatives that have greater impacts on respiration, and dexmedetomidine may potentiate the respiratory depressant effects of these drugs. Therefore, caution is warranted when dexmedetomidine is used to treat patients at high risk for respiratory complications.

2.3.6 Effects on renal function

In animal studies, administration of dexmedetomidine has been shown to inhibit vasopressin secretion and to enhance diuresis already at low doses. It has been postulated that these actions may possibly protect the kidneys from ischemic insults (Villela et al. 2005).

Diuresis-enhancing effects of dexmedetomidine have been reported also in humans, but the evidence is rather weak since the conclusions are based on only a few case reports (Ji et al. 2013, Pratt et al. 2013, Kirschen et al. 2019).

2.3.7 Other effects - intraocular pressure, shivering, delirium, blood platelets

α_2-Adrenoceptor agonists (e.g. brimonidine) are used as eye drops to treat intraocular hypertension (Oh et al. 2018). It is well known that intubation increases intraocular pressure in anesthetized patients (Shribman et al. 1987) and therefore the effect of dexmedetomidine on intraocular pressure during intubation has been evaluated. It

has been shown that dexmedetomidine can lower intraocular pressure of intubated patients under general anesthesia (Zhou et al. 2017).

Dexmedetomidine and clonidine are known to modulate thermoregulation, and their effects on postoperative shivering have been investigated (Horn et al. 1997, Pitoni et al. 2011). Postoperative shivering can evoke uncomfortable sensations that may trigger complications such as tachycardia, hypertension, and cardiac ischemia (Zhen-Xiu et al. 2015). Thus, attenuation of postoperative shivering could be a favourable way to reduce oxygen consumption. However, the hypothermia-promoting effects of α_2-adrenoceptor agonists need to be taken into account when treating patients with dexmedetomidine. It has been found that α_2-adrenoceptor agonists are able to disturb thermoregulatory control mechanisms by lowering the thresholds for vasoconstriction and shivering without affecting the sweating threshold (Talke et al. 1997). In addition, many animal studies have demonstrated that α_2-adrenoceptor agonists have hypothermic effects (Lähdesmaki et al. 2003, Gilsbach et al. 2009).

Human blood platelets express α_{2A}-adrenoceptors, and their activation enhances platelet aggregation (Lanza and Cazanave 1985). Kawamoto et al (2015) investigated the effects of dexmedetomidine on human platelets *in vitro* by using the somewhat non-selective α_2-adrenoceptor antagonist, yohimbine, to block α_2-adrenoceptor activation. They found that dexmedetomidine had bidirectional effects on human platelet functions, i.e. enhancing aggregation through α_{2A}-adrenoceptors but conversely exerting suppressive effects which were mediated via putative I_1-imidazoline receptors (Kawamoto et al. 2015). A recent study found that dexmedetomidine had no effects on human platelet function when this was evaluated with thromboelastography (Yoshikawa et al. 2018). Thus, the possible effects of dexmedetomidine on platelet aggregation in humans appear to be clinically insignificant.

The effects of dexmedetomidine on the risk and occurrence of delirium have been investigated in ICU patients and in perioperative patient care. A recent meta-analysis showed that in comparison with traditional sedatives, dexmedetomidine reduced delirium and agitation in ICU patients (Ng et al. 2019). Postoperative administration of dexmedetomidine has also been claimed to reduce delirium in surgical patients, particularly following cardiac surgery (Pavone et al. 2018). The possible effects of intraoperatively administered dexmedetomidine on postoperative cognitive dysfunction were evaluated in elderly non-cardiac surgical patients, but the results were inconclusive (Zhang et al. 2018).

2.4 Dexmedetomidine in pediatric patients

2.4.1 Pediatric ambulatory sedation

Most pediatric patients undergoing surgical or other invasive procedures need sedation (Mahajan et al. 2014). Children are often frightened by the unfamiliar environment, strange people, and perhaps painful procedures, and do not understand why they are undergoing investigations or procedures and must remain confined. Even if many uncomfortable sensations and experiences can be attenuated with good personal care and the use of sedative and analgesic medications, all drugs have their own adverse effects and the pediatric anesthetist must be aware of these properties. Thus, there is a need for improving sedative regimens that provide comfortable experiences without any increased risk of complications (Hayden et al. 2016).

$GABA_A$ receptor modulators such as propofol, midazolam and barbiturates are the traditional sedative agents that are used in ambulatory sedation of pediatric patients (Hansen 2015). All of these agents are highly amnestic and carry a risk of respiratory and cardiovascular depression. The amnestic properties of $GABA_A$ modulators may be favourable in ambulatory sedation but carry a risk for loss of cooperation and poor arousability. Ketamine is another traditional sedative agent that is used in sedation of pediatric subjects (Gyanesh et al. 2014). Its benefits over $GABA_A$ modulators include its minimal effects on respiration and hemodynamics. Moreover, ketamine is a relatively potent analgesic agent. Unfortunately, when used alone for sedation of pediatric patients, ketamine has been associated with the occurrence of hallucinations and nightmares and also with excessive salivation. Thus, it is recommended that ketamine should be used together with another sedative agent (e.g. midazolam) in order to reduce the risk of these side effects (Yang et al. 2019).

In spite of the availability of many sedative agents that can be used safely and efficiently in the ambulatory sedation of pediatric patients, a single optimal sedative agent is still lacking.

2.4.2 Use of dexmedetomidine in children

Dexmedetomidine has marketing authorization only for adult patients and the use of dexmedetomidine in pediatric patients is off-label. Dexmedetomidine appears to have many favourable properties for use as a pediatric sedative agent, such as the fact that it exerts only marginal effects on respiration. In fact, it has been widely used in pediatric intensive care, as an anesthetic adjunct and as premedication (Tobias and Berkenbosch 2008, Mason and Lerman 2011).

The use of dexmedetomidine in the ambulatory sedation of pediatric patients is rather common, particularly in the sedation of children undergoing magnetic resonance imaging (MRI). Conventional MRI sedation of pediatric patients has been attempted with propofol, barbiturates, benzodiazepines, chloral hydrate, ketamine, remifentanil or sevoflurane; most of these compounds may cause respiratory depression or hypotension, which in extreme cases can be harmful to the child (Starkey et al. 2011, Hansen et al. 2015, Pedersen et al. 2013). An ideal sedation protocol should have minimal effects on respiration and hemodynamics, keep the child calm and immobile during the procedure, but allow rapid recovery and discharge. While dexmedetomidine may possess many of these favourable properties, its optimal dosage for MRI sedation still remains unknown.

Various dose regimens of dexmedetomidine have been employed in pediatric patients. Recommended adult doses vary from 0.5 to 1.4 μg/kg. In children, intravenous doses are typically higher, even up to 2.5 μg/kg. Recent reports indicate that very high doses of dexmedetomidine (up to 9 μg/kg intravenously delivered over 30 min) can be safely administered to children aged 2 to 6 years (Mason et al. 2010). On the other hand, the cardiac output of neonates and infants is highly dependent on HR (Winberg et al. 1992). Thus, the hemodynamic effects of dexmedetomidine should be taken account and closely monitored when administering the drug to children.

The effects of dexmedetomidine infusions lasting over three days have been studied in critically ill pediatric patients. After addition of dexmedetomidine to the treatment, patients were more comfortable as evidenced by decreasing Comfort-B scores (CBSS). The hemodynamic effects of dexmedetomidine did not limit its long-term use, but withdrawal from dexmedetomidine was, however, associated with agitation, tremors, and decreased sleep (Whalen et al. 2014). There is also some experience of the use of dexmedetomidine in critically ill neonates and infants. It has been recommended that administration of dexmedetomidine in these patients should be very cautious because of their potentially inadequate capacity of glucuronidation and poorly developed drug metabolism. Thus, especially in newborns, the drug dosage may have to be lower than in older children and adults (Estkowski et al. 2015).

2.5 Extravascular administration of dexmedetomidine

2.5.1 Introduction to extravascular administration

Although dexmedetomidine is only registered for intravenous use, multiple alternative routes of administration have been investigated. The rationales for extravascular administration include ease of administration in certain patient

populations and clinical settings and the possibility to avoid the high peak plasma levels encountered after intravenous administration. Another advantage of extravascular administration is the lack of need for intravenous access. This can improve patient satisfaction e.g. in the pediatric patient population.

The examples given below show that regardless of the route of administration, similar adverse effects may occur as are present after intravenous administration. However, these effects are likely to be attenuated in comparison with intravenous administration.

2.5.2 Intranasal administration

Of the different extravascular routes of administration of dexmedetomidine that have been investigated, the intranasal route appears to be the most popular and feasible. There are some systematic reviews on the effects of intranasal dexmedetomidine in children, but only three small pharmacokinetic studies have been published describing intranasal administration of dexmedetomidine in children and adults.

In the study of Iirola et al (2011), six healthy male adult volunteers received 84 µg of intranasal and 84 µg of intravenous dexmedetomidine. Systemic bioavailability of the intranasal spray formulation was variable, ranging from 35% to 93% in the individual subjects, with a mean bioavailability of 65%. Heart rate was significantly lower during the initial 0- to 30-min period after intravenous administration in comparison to the corresponding situation when the drug was delivered intranasally, but there was no statistically significant difference over the 0- to 10-h period. Systolic and diastolic blood pressures were similar regardless of the administration route (Iirola et al. 2011a).

Li et al. (2018) compared approximately 1 µg/kg doses of dexmedetomidine administered either as intranasal drops or with an intranasal atomizer as well as the same dose intravenously during three separate sessions in eight healthy adult volunteers. The mean bioavailability of intranasal dexmedetomidine was found to be 41 to 65%. The onsets of effects were at 15, 48 and 60 min after intravenous dosing, intranasal spray and intranasal drops, respectively. There were no significant differences in the duration of sedation (Li et al. 2018).

Miller et al. (2018) evaluated the pharmacokinetics of intranasally delivered dexmedetomidine in pediatric patients (age 6-44 mo) undergoing cardiopulmonary bypass. Six patients received 1 µg/kg and six patients received 2 µg/kg of intranasal dexmedetomidine, and another six patients received 1 µg/kg of intravenous

dexmedetomidine. Median peak concentrations of dexmedetomidine were 0.2 and 0.36 ng/ml and median times to peak concentration were 47 minutes and 46 minutes after the two different intranasal dosages. The relative bioavailability of intranasal dexmedetomidine appeared to be 84% (Miller et al. 2018).

2.5.3 Intramuscular administration

Intramuscularly administered dexmedetomidine appears to have good bioavailability and may be used when the drug is to be given as a single dose. Scheinin et al. (1992) compared single intramuscular doses of dexmedetomidine (0.5, 1.0, and 1.5 µg/kg) to placebo in six healthy subjects in a single-blind crossover study. A linear one-compartment open model was used to calculate pharmacokinetic parameters. Compared to placebo, up to 22% decreases in systolic and diastolic blood pressure were seen, with maximal effects observed between 90 and 150 minutes after drug administration. There was no clear dose dependency of the hypotensive effect, with the 1.0 and 1.5 µg/kg doses having rather similar effects (Scheinin et al. 1992).

In a randomized, controlled multi-center study, single doses of intramuscular dexmedetomidine were administered to ASA 1-2 patients undergoing elective abdominal hysterectomy, cholecystectomy or intraocular surgery. Pretreatment with a single intramuscular injection of 2.5 µg/kg dexmedetomidine induced comparable sedation and anxiolysis as an intramuscular injection of 0.08 mg/kg midazolam. Compared to midazolam, patients receiving dexmedetomidine for premedication required 56% less fentanyl intraoperatively. The use of dexmedetomidine as a premedication increased the incidence of intraoperative hypotension and bradycardia (Scheinin et al. 1993).

Intravenous and intramuscular administration of dexmedetomidine has been examined in healthy male volunteers with ten subjects receiving 2.0 µg/kg via both routes. Five minutes after intravenous dosing, there was a 22% mean increase in MAP and a 27% mean decrease in HR. These kinds of early hemodynamic effects were not seen after intramuscular administration. During the 4 h follow-up after the intramuscular dose, MAP decreased by 20% and HR was reduced by 10% (Dyck et al. 1993a).

In the trial conducted by Anttila et al. (2003), 2.0 µg/kg doses of dexmedetomidine were given intravenously, intramuscularly, per orally and buccally to 12 healthy male subjects. Compared to intravenous administration, intramuscular injection appeared to have complete bioavailability, with relative AUC values in the range of 96–112%. Hemodynamic or other effects were not described in that study report (Anttila et al. 2003).

2.5.4 Buccal and oral administration

In the above-mentioned study of Anttila et al. (2003), oral administration of 2.0 µg/kg doses of dexmedetomidine displayed poor bioavailability in a range of 12-20%, but buccally administered doses were well absorbed, with the dose-corrected bioavailability in a range of 73–92%. (Anttila et al. 2003).

2.5.5 Other routes of administration

The use of subcutaneous administration of dexmedetomidine in humans has earlier been reported in only one case report, where dexmedetomidine was administered subcutaneously in the palliative care of a dying adult patient (Hilliard et al. 2015).

Kivistö et al. (1994) compared the pharmacokinetics of transdermally and intravenously administered dexmedetomidine in healthy volunteers. The transdermal preparation, containing 625 µg of dexmedetomidine base, was applied to the skin for 12 h. The intravenous dose (2.0 µg/kg as dexmedetomidine hydrochloride) was administered as an infusion over 5 min. The mean relative systemic bioavailability of dexmedetomidine from the transdermal preparation was 51%, but the proportion of dexmedetomidine released from the preparation was 88%. The mean terminal half-life was 3.1 h after intravenous dosing and 5.6 h after transdermal administration. With the transdermal administration, the mean maximal reductions in blood pressure (systolic/diastolic) and HR were 28/20 mmHg, and 19 bpm. Sedative effects were observed 1-2 h after the start of transdermal administration (Kivistö et al. 1994).

Zanaty et al. (2015) compared the pharmacodynamics of inhaled nebulized dexmedetomidine (2 µg/kg), nebulized ketamine (2 mg/kg) and their combination (1 µg/kg and 1 mg/kg) in children undergoing dental surgery. Sedative effects were recorded 30 min after administration of nebulized dexmedetomidine with the most satisfactory sedation being observed after administration of the dexmedetomidine/ketamine combination (Zanaty et al. 2015).

2.6 Pharmacometric modeling of dexmedetomidine

2.6.1 Introduction to pharmacometric modeling

Understanding of dose–concentration–effect relationships is a fundamental component of clinical pharmacology. In traditional pharmacokinetic studies, a sufficient number of samples must be collected to allow a reliable pharmacokinetic analysis to be performed on an individual subject basis, irrespective of whether that analysis is a simple computation of non-compartmental parameters or a more

sophisticated estimation of the parameters of a pharmacokinetic model through nonlinear regression or other numerical analysis techniques (Standing et al. 2017). Data are considered “sparse” when an insufficient number of samples have been collected in an individual to allow relevant pharmacokinetic analysis to be performed for that individual (Owen and Fielder-Kelly 2014).

The traditional method of pharmacokinetic data analysis uses a two-stage approach. The first stage involves an estimation of the pharmacokinetic parameters by conducting a nonlinear regression using the individual's drug concentration-time data. Individual parameter estimates obtained during the first stage serve as input for the second-stage calculation of descriptive summary statistics on the sample, typically, mean parameter estimates, variance and covariance of the individual parameter estimates (Mould et al. 2013). This method encounters inherent problems due to errors in dosing compliance, missing samples, and other data errors that are present, resulting in biased parameter estimates. Therefore, this two-stage approach is no longer in use; nonetheless many earlier studies have employed it and these deficiencies should be taken into account when interpreting previous results.

Population pharmacokinetic-phamacodynamic methodology involves the application of the concepts of non-linear mixed effects modeling to model unexplained inter- and intra-individual variability (Mould and Upton, 2012). A mixed-effects model is a statistical model that incorporates both fixed effects and random effects. Fixed effects are population parameters assumed to be the same each time when data are collected, and random effects are random variables associated with each sample (individual) from a population. Mixed-effects models can be developed with small sample sizes and sparse data sets, and are often used to draw inferences on features underlying profiles of repeated measurements from a group of individuals from a population of interest (Mould et al. 2013).

Pharmacometric models account for the general structure of the underlying system, and a set of hierarchical variability components between subjects, within subjects over time and between observation variability (Mould and Upton, 2013; Upton and Mould, 2014). The analysis of pharmacokinetic and pharmacodynamic data includes mathematical models of pharmacology, disease, biology and physiology for describing and quantifying interactions, both beneficial and deleterious, between xenobiotics and patients (Barrett et al. 2008). Pharmacometric approaches are further used to elucidate the effects of covariates. This results in the creation of models which can be used in simulations that make inferences on optimum dosing for clinical practice (Standing et al. 2017).

The general model strategy is first to develop a structural model that explains the population trend in the dose-concentration-effect relationship. Previous knowledge about the drug substance and on human physiology is used to build a structural model. Then, a statistical model is developed and incorporated into the structural model to explain the between-subject and residual variability in the data. Finally, the influence of observable patient characteristics (covariates) such as body weight and age on the different model parameters are explored and incorporated into the model as predictors of clinical relevance. The predictive capability of the final model is assessed by visualizing the correlation between observations and model predictions using graphical analysis. The biological plausibility of the parameter estimates and their uncertainty are assessed by using simulation-based diagnostics, such as bootstrap or sampling-importance-resampling procedures (Owen and Fielder Kelly 2014).

Frequently obtained samples and observations from actual patients compatible with clinical care can be used instead of designing a specific experimental setting which minimises the burden for each individual subject. Importantly, the obtained information may often be directly applied into clinical practice (Vermeulen et al. 2017). It has been stated that pharmacometric models should be employed in model-informed precision dosing (MIPD) to improve drug therapy by estimating the optimal dose for an individual patient. MIPD aims to improve therapeutic outcomes in patients by searching for the optimal balance between efficacy and toxicity. The approach is based on the available information about the patient, the disease for which they are treated, the presence of comorbid diseases, and the drug therapies they are receiving. MIPD is inclusive of various modeling approaches including pharmacometrics.

2.6.2 Pharmacokinetic models of dexmedetomidine

Several pharmacokinetic models have been developed for dexmedetomidine. In most studies, a two-compartment pharmacokinetic model with zero order input to and linear elimination from the central compartment has been used to describe dexmedetomidine disposition and elimination, whereas four studies found a three-compartment pharmacokinetic model to be more appropriate (Dyck et al. 1993b, Dutta et al. 2000, Lin et al. 2011, Hannivoort et al. 2015, Kuang et al. 2016). Two studies employed one-compartment models to describe the pharmacokinetics of dexmedetomidine (Välitalo et al 2015, Greenberg et al. 2017). An overview of published population-based pharmacokinetic dexmedetomidine models in adult and pediatric populations is presented in Tables 3 and 4.

Table 3. Overview of published population pharmacokinetic dexmedetomidine models in the adult population.

Study (year)	N	Patient population	No. of samples	Last sample (h)	Dexmedetomidine administration	Tested Covariates	Covariate models
Dyck 1993	16	Male healthy volunteers	14	2	IV TCI	Age, weight, height	3 -CMT with height as a covariate on CL
Talke 1997	8	Female postoperative patients	8	3	IV TCI	Age, weight, height	2-CMT with no relationship between covariates
Dutta 2000	10	Healthy male volunteers	10	4	IV TCI	CO	2-CMT with CO as covariate on CL
Venn 2002	10	Postoperative ICU patients	10	12	IV infusion with a loading dose	None	2-CMT with no tested covariates reported
Lin 2011	22	Chinese postoperative patients	24	12	IV infusion with a loading dose	Age, weight, height, sex, BMI, LBM	3-CMT with height as a covariate on CL
Iirola 2012	21	Critically ill patients	11	100-550	IV infusion with a loading dose	Age, weight, height, sex, BMI, LBM	2-CMT with age as a covariate on CL and ALB on V2
Lee 2012	24	Korean healthy volunteers	13	12	IV infusion with a loading dose	Age, weight, serum creatinine, LT, albumine	2-CMT with ALB as a covariate on CL and age on V1
Välitalo 2013	527	Critically ill patients	2-3	48	IV infusion with a loading dose	Age, weight, CC, bilirubin, LT, ALB	1-CMT with weight as a covariate on CL and ALB on V1
Cortinez 2015	40	Obese and non-obese laparoscopic surgery patients	21	6	IV infusion with a loading dose	Age, weight, fat free mass, normal fat mass	2 CMT with FFM as a covariate on CL, Q2, V1 and V2,
Hannivoort 2015	18	Healthy volunteers	14	5	IV TCI	Age, weight, height, BMI, sex	3-CMT with a weight as a covariate on CL, Q2, Q3, V1, V2 and V3
Kuang 2016	35	Chinese patients undergoing spinal anesthesia	15	10	IV infusion with a loading dose	Age, weight, height, sex, BMI, LT, CC	3-CMT with ALT as a covariate on CL, age on V1 and weight on V2

Study (year)	N	Patient population	No. of samples	Last sample (h)	Dexmedetomidine administration	Tested Covariates	Covariate models
Zhong 2018	23	Patients with normal renal function and patients with end-stage renal disease	13	8	IV infusion	Age, weight, height, sex, BMI, LBM, BSA, ALB, renal function	2-CMT with no relationship between covariates
Smuszkiewicz 2018	27	Critically ill patients	14	24-102	IV infusion	Age, weight, sex, SOFA, infusion duration, use of inotropes	2-CMT with no relationship between covariates
Rolle 2018	40	Obese and non-obese patients undergoing laparoscopic surgery	18	12-20	IV infusion with a loading dose	weight, LBM, ABW, hepatic blood flow, liver steatosis, ALT	2-CMT with hepatic blood flow as a covariate on CL

ABW; adjusted body weight, ALB; serum albumine, ALT; alanine transaminase, AST; aspartate transaminase, BSA; body surface area, CC; creatinine clearance, CL; clearance, CMT; compartment model, CO; cardiac output, IV; intravenous, LBM; lean body mass, SOFA; sequential organ failure assessment score TCI; target controlled infusion

*Modified from Weerink et al. 2017

Table 4. Overview of published population pharmacokinetic dexmedetomidine models in the pediatric population.

Study (year)	N	Patient population	No. of samples	Last sample (h)	Dexmedetomidine administration	Tested Covariates	Covariate models
Potts 2009	95	Pediatric ICU patients	4	8	IV infusion with a loading dose	Age, weight, cardiac surgery, arterial/venous sampling, study site	2-CMT with age, weight and postcardiac surgery state as covariates on CL and weight as a covariate on Q2, V1 and V2
Su 2010	36	Pediatric cardiac postoperative patients	13	24	IV infusion with a loading dose	Age, weight, cardiopulmonary bypass time, ventricular physiology	2-CMT with age and ventricular physiology as covariates on CL
Liu 2016	39	Pediatric general surgery patients	13	8	IV infusion	Age, weight, BMI, sex, LBM	2-CMT with weight as a covariate on CL, Q2, V1 and V2
Su 2016	59	Neonatal and pediatric postoperative patients	6-14	18	IV infusion with a loading dose	Age, weight, total cardiopulmonary bypass time, ventricular physiology	2-CMT with age, weight, total bypass time and ventricular physiology as covariates on CL and weight as a covariate on Q2, V1 and V2
Wiczling 2016	38	Critically ill pediatric patients	15	6	IV infusion	Age, weight, cardiac surgery, arterial/venous sampling, study site	2-CMT with age and weight as a covariate on CL and weight on Q2, V1 and V2
Greenberg 2017	20	Pre-term and term infants	5-10	250-1500	IV infusion	Age, weight	1-CMT with age and weight as a covariate on CL and weight on Vd
Perez-Guille 2018	30	Ambulatory pediatric patients	14	10	IV infusion	Age, weight	2-CMT with weight as a covariate on CL

Study (year)	N	Patient population	No. of samples	Last sample (h)	Dexmedetomidine administration	Tested Covariates	Covariate models
Damian 2018	20	Children and infants undergoing liver transplantation	20	72	IV infusion with a loading dose	Age, weight, liver ischemia time, donor age, liver type, INR, bilirubin, ALT, AST	2-CMT with weight as a covariate on CL
Miller 2018	18	Pediatric patients undergoing cardiopulmonary bypass	8	2	IV 10 min bolus or intranasal bolus	Age, weight	2-CMT with weight as a covariate on CL

ALB; serum albumine, ALT; alanine transaminase, AST; aspartate transaminase, BSA; body surface area, CL; clearance, CMT; compartment model, CO; cardiac output, INR; international normalized ratio, IV; intravenous, LBM; lean body mass

*Modified from Weerink et al. 2017

2.6.3 PK/PD models of dexmedetomidine

Very few models have described dexmedetomidine PK/PD relationships. Yoo et al. (2015) developed a mechanism-based population PK/PD model for the cardiovascular and central nervous system effects of intravenously and intranasally administered dexmedetomidine in healthy subjects. The comprehensive panel of two biomarkers and seven response measures were well captured by the population PK/PD models. The subjects were more sensitive to the central nervous system effects (smaller EC_{50} values) than to the cardiovascular effects of dexmedetomidine (Yoo et al. 2015).

Colin et al. (2017a, 2017b) published two models based on an earlier PK model. Dexmedetomidine was given to healthy volunteers using the model published by Dyck et al. (1993) with different dexmedetomidine target concentrations and two PK/PD models were created without blood sampling. The first model described dexmedetomidine-induced hypotension, hypertension and bradycardia, whereas the second described the sedative properties of dexmedetomidine utilizing the bispectral index and a Modified Observer´s Assessment of Alertness/Sedation (Colin et al. 2017a, Colin et al 2017b).

Li et al. (2018) conducted a PK/PD analysis of intravenously and intranasally administered dexmedetomidine in eight healthy human volunteers on three separate sessions. A two-compartment disposition model was used in the pharmacokinetic analysis, and the effect of dexmedetomidine on sedation was modelled with a sigmoidal E_{max} model driven by an effect compartment. The effect compartment had an equilibration half-time of 3.3 min and the EC_{50} in plasma was estimated to be 903 pg/ml (Li et al. 2018).

Recently, the peripheral vasoconstrictive effect of dexmedetomidine was evaluated. Dexmedetomidine was administered as intravenous target-controlled infusion (TCI) to ten healthy volunteers and arterial blood samples were collected for analysis of plasma dexmedetomidine concentration. Sympathetic nerve fibers were blocked unilaterally with a brachial plexus block and peripheral vasoconstrictive effects of dexmedetomidine were assessed using photoelectric plethysmography (Talke et al. 2018). An overview of the PK/PD models of dexmedetomidine is presented in Table 5.

Table 5. Overview of published dexmedetomidine PK/PD models in the adult population.

Study (year)	N	Patient population	No. of samples	Last sample (h)	Dexmedetomidine administration	Model properties
Yoo 2015	6	Healthy volunteers	15	10	IV 10 min bolus or intranasal bolus	2-CMT with E_{max} model for noradrenaline release and hemodynamic effects
Colin 2017	35	Healthy volunteers	0**	-	IV TCI	E_{max} model for bispectral index and Modified Observer's Assessment of Alertness/Sedation
Colin 2017	23	Healthy volunteers	0**	-	IV TCI	E_{max} model for mean arterial pressure and heart rate
Li 2018	8*	Healthy volunteers	12	8	IV 10 min bolus, IN spray, IN drops	2-CMT with E_{max} model for Ramsey sedation score
Talke 2018	10	Healthy volunteers	14	1,25	IV TCI	3-CMT with E_{max} model for vasoconstriction

ALB; serum albumin, ALT; alanine transaminase, AST; aspartate transaminase, BSA; body surface area, CC; creatinine clearance, CL; clearance, CM; compartment model, CO; cardiac output, Emax; maximal effect of dexmedetomidine, IV; intravenous, LBM; lean body mass, TCI; target controlled infusion

*On three separate sessions, ** pharmacokinetic model was based on TCI target concentrations

III AIMS OF THE STUDY

The present series of clinical investigations was conducted with the overall aim to acquire an improved understanding of the alternative, extravascular routes of administration of dexmedetomidine and of the pharmacokinetics and pharmacological effects of dexmedetomidine in pediatric patients. Specifically, the individual aims of the different sub-projects were as follows:

1. To determine the pharmacokinetics of subcutaneously administered dexmedetomidine in healthy adult volunteers.

2. To build a PK/PD model of subcutaneously administered dexmedetomidine in healthy adult volunteers.

3. To clarify the pharmacokinetics and effects of intranasally delivered dexmedetomidine in pediatric patients undergoing MRI imaging.

4. To evaluate the barbiturate-sparing effect of intranasally administered dexmedetomidine in pediatric patients undergoing MRI imaging.

5. To examine whether intranasal low-dose dexmedetomidine possesses postoperative opioid-sparing properties in adult surgical patients.

IV MATERIALS AND METHODS

4.1 Subjects

4.1.1 Study participants

Altogether 10 healthy male volunteers, 255 pediatric patients and 120 adult patients participated in Studies I, II-III and IV, respectively. The number of subjects and their demographics are presented in Table 6.

Table 6. Characteristics of the subjects in studies I-IV and subsequent publications.

	Study I		**Study II**	**Study III**	**Study IV**
	Study Ia	Study Ib			
Name of the study	SCDEX	SCDEXMOD	PINDEX	TIODEX	PROTEDEX
Number of participants	8	10	55	200	120
Study design	Prospective	Prospective	Prospective	Retrospective	Retrospective
Dexmedetomidine dose	1 µg/kg	1 µg/kg	2-3 µg/kg	3 µg/kg	0.5-1.0 µg/kg
Administration route	IV, SC	IV, SC	IN	IN	IN
Age (yr)	23.0 (2.3)	22.6 (2.2)	5.0 (2.4)	4.5 (2.6)	67 (9.0)
BMI (kg/m^2)	24.2 (1.6)	23.9 (1.5)	16.3 (2.2)	16.5 (2.2)	27.5 (3.6)
Weight (kg)	78.4 (6.9)	79.9 (7.1)	19.9 (6.9)	18.8 (7.5)	78.4 (12.0)
Publication	I	II	III	IV	V

Age, height and weight are expressed as mean and SD. IV; intravenous, SC; subcutaneous, IN; intranasal, BMI; body mass index

4.1.2 Inclusion and exclusion criteria

In Study I, healthy, non-smoking male volunteers aged between 18 and 30 years were recruited via internet advertisements directed to university students. After obtaining written informed consent, subject eligibility was evaluated by examining their medical history and a physical examination as well as laboratory screening tests.

In Studies II and III, pediatric patients aged between 1 month and 11 years were included if they had normal developmental status and were scheduled for MRI requiring sedation or anesthesia at Turku University Hospital. In Study II, informed consent was obtained from all guardians and patients (if relevant).

In Study IV, one hundred and twenty patients with ASA status 1-2, age between 35 and 80 years, weight between 50 and 100 kg and scheduled for primary unilateral hip arthroplasty under total intravenous anesthesia were included. According to Finnish law and Ethics committee of South-West Finland Hospital District Studies III and IV did not require consent from patients to participate.

4.1.3 Exclusion criteria of studies I-IV

Exclusion criteria of all studies included existing or recent significant disease that could influence the study outcome or cause a health hazard for the subject during the study, clinically significant abnormal findings in physical examination or laboratory screening, previous history of intolerance to the study drug or to related compounds and additives, prior drug therapy with dexmedetomidine in the 14 days prior to the study, use of any drugs (e.g. CYP inducers or inhibitors) known to cause enzyme induction or inhibition for a period of 30 days prior to the study and participation in any other clinical study involving investigational or marketed drug products concomitantly or within one month prior to the entry into this study. Patients receiving any medications other than paracetamol or adjuvant analgesics that could affect the study outcome were further excluded from studies I and IV.

4.2 Study designs

4.2.1 Pharmacokinetic studies (I-II)

Study I was an open two period study with a cross-over design and balanced randomization. The wash-out period between consecutive administrations was at least 3 weeks. Eleven volunteer subjects compatible with the inclusion and exclusion criteria were entered into the study after informed consent. Figure 5 illustrates the study schedule.

Study II was an open prospective one period study. Patients potentially eligible for the study were approached for information, preliminary assessment of eligibility criteria and consent either during their preoperative visit or upon arrival at the hospital for the procedure. Written informed consent was obtained from the patients

(if applicable) and their guardians before any study-specific procedures were carried out. Figure 5 illustrates the study procedures.

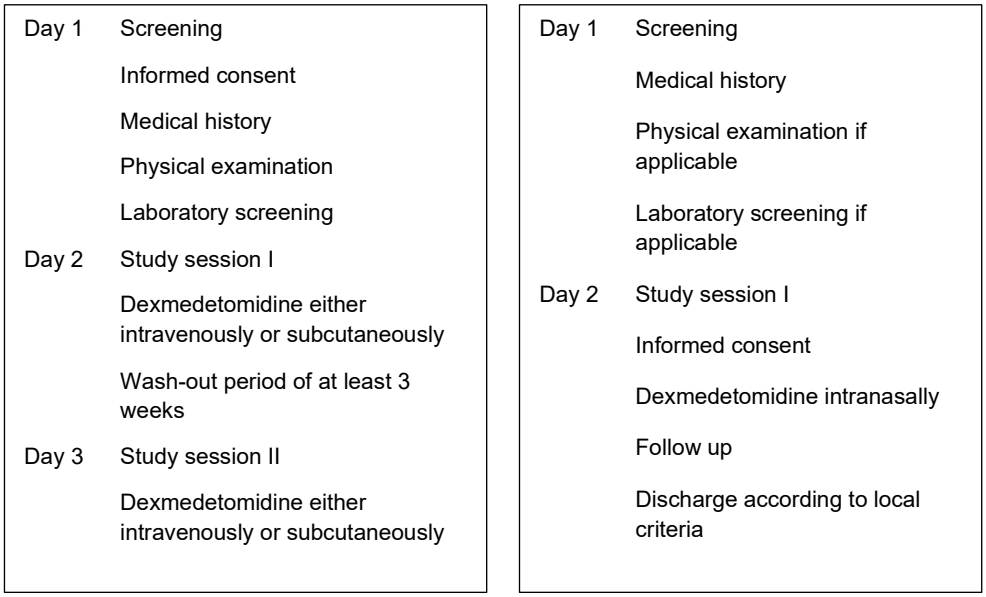

Figure 5. Study setting of the study I (left) and study II (right).

4.2.2 Pharmacodynamic studies (III-IV)

In Studies III and IV, eligible patients were identified and patient data were retrieved from the anesthesia reports and the patient database of the hospital. Study III was a comparative retrospective study, where 200 pediatric patients undergoing MRI were examined. Half of the patients were consecutive pediatric patients receiving 3 μg/kg of intranasal dexmedetomidine 45-60 min before the MRI procedure while the rest were 100 consecutive patients receiving only thiopental for MRI sedation. Sedation was maintained with intravenous thiopental when applicable. Thiopental consumption was analyzed for both groups.

Study IV was a comparative retrospective study, where 120 patients undergoing unilateral hip arthroplasty under general anesthesia were included. Half of the patients were consecutive patients receiving 50 μg of intranasal dexmedetomidine after anesthesia induction; the others were 60 consecutive patients receiving conventional general anesthesia without dexmedetomidine. HR and MAP were recorded continuously during the operation and in the PACU. Postoperative opioid consumption was analyzed for both groups.

4.3 Dexmedetomidine dosing

In Study I, healthy volunteers were scheduled to receive 1 μg/kg of dexmedetomidine intravenously and subcutaneously in a randomized order. Intravenous and subcutaneous doses of dexmedetomidine were administered at concentrations of 8 μg/ml and 50 μg/ml during 10 min by infusion with the same pump. There were no prior studies on subcutaneous administration of dexmedetomidine, but the dosage used in our study was based on similar studies where dexmedetomidine had been administered intramuscularly or intranasally (Scheinin et al 1992, Iirola et al. 2011a).

In Studies II and III, pediatric patients received 2-3 μg/kg doses of dexmedetomidine intranasally 45-60 min before the scheduled MRI procedure. Dexmedetomidine (Dexdor®100 μg/ml, Orion Pharma, Espoo, Finland) was administered intranasally in the semi-recumbent position using a LMA MAD Nasal™ device (Teleflex MAD Nasal, NC, USA) (Figure 6). The dexmedetomidine dosage used in this study was based on previous reports (Mason et al. 2008, Siddappa et al. 2011, Mason et al. 2010) which had determined the safety of dexmedetomidine at doses up to 9 μg/kg given intravenously over 30 min.

In Study IV, adult patients undergoing hip arthroplasty under general anesthesia were scheduled to receive 50 μg of dexmedetomidine intranasally after anesthesia induction. Intranasal dexmedetomidine was administered in the supine position with the MAD device. Dexmedetomidine dosage was according to a local protocol based on previous reports (Xu et al. 2014) which had confirmed the safety of dexmedetomidine at doses up to 1 μg/kg given intravenously over 10 min to patients undergoing hip arthroplasty.

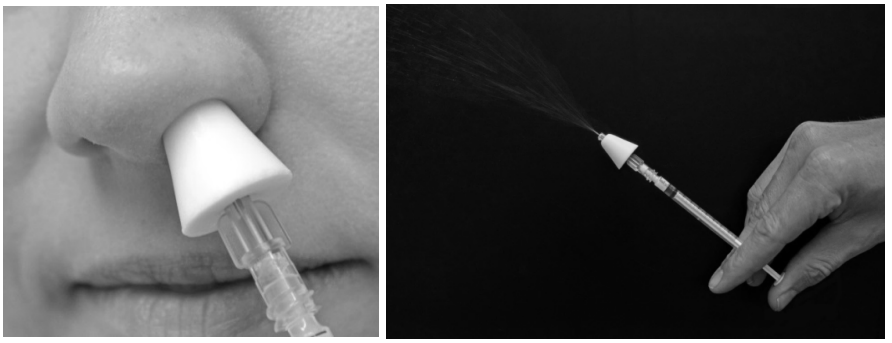

Figure 6. MAD nasal spray device.

4.4 Blood sampling and analysis of dexmedetomidine and catecholamine concentrations

4.4.1 Blood sampling

Blood samples for plasma dexmedetomidine and/or catecholamine analysis were drawn in Studies I and II. In Study I, arterial blood samples (blood volume 5 ml) were collected immediately prior to administration of dexmedetomidine (baseline) and thereafter at 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2 and 3 h into EDTA tubes for the determination of concentrations of dexmedetomidine, adrenaline and noradrenaline in plasma. Further blood samples were collected at 4, 5, 6, 8 and 10 h after dexmedetomidine administration for the determination of dexmedetomidine.

In Study II, venous blood samples (blood volume 1 ml) were collected during the assumed absorption phase, i.e. 10 and 20 min after drug administration, two additional samples were drawn 30 and 45 min after drug administration and finally two samples were drawn between 120 and 240 min, during the assumed elimination phase after intranasal administration of dexmedetomidine into micro EDTA tubes for the determination of dexmedetomidine plasma concentrations. A 5 min time window was allowed in sampling times for the first three samples. A 10 min window was allowed for the fourth blood sample. Two blood samples were collected between 120 and 240 min from drug administration in order to avoid blood sampling during MRI imaging. Actual sampling times were recorded and used in the data analysis.

4.4.2 Analysis of drug and catecholamine concentrations in plasma

In Studies I-II, concentrations of dexmedetomidine in plasma were determined with a validated (Guidance for Industry Bioanalytical Method Validation) reversed-phase high-performance liquid chromatography method with tandem mass spectrometric detection (HPLC-MS/MS; Shimadzu Prominence HPLC connected to an AB Sciex API4000 mass spectrometer), with some modifications to a previously described procedure (Ji et al. 2004). The lower limit of quantitation (LLOQ) was 0.05 ng/ml. The within- and between-run precision of the assay (coefficient of variation) was within 5% in the relevant concentration range. Concentrations of adrenaline and noradrenaline in plasma were measured in study I using HPLC and coulometric electrochemical detection, basically as described previously (Scheinin et al 1991), but now adapted to a dedicated HPLC system provided by Thermo Fisher Scientific (Waltham, MA, USA). The LLOQ for both catecholamines was 0.1 nM. The within- and between-run precision of the assay (coefficient of variation) was within 10% in the relevant concentration range.

4.5 Pharmacokinetic analysis and pharmacometric modeling

4.5.1 Non-compartmental analysis

In Studies I and II, the peak dexmedetomidine concentration (C_{max}) and the corresponding time points (T_{max}) were directly observed from the data. For each subject, the terminal log-linear phase of the plasma dexmedetomidine concentration-time curve was identified visually, and the elimination rate constant (k_{el}) was determined by regression analysis on the basis of at least four time points. The elimination half-life ($t_{1/2}$) was then calculated from the equation $t_{1/2} = \ln 2 / k_{el}$. The area under the dexmedetomidine plasma concentration-time curve (AUC) was calculated using the trapezoidal method, with the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Apparent clearance (CL/F) and apparent volume of distribution of dexmedetomidine during the elimination phase (Vz/F) were also calculated, with non-compartmental methods based on the statistical moment theory. The pharmacokinetic analysis was carried out with WinNonlin software (version 4.1, Pharsight Corporation, Mountain View, CA, USA).

4.5.2 Pharmacometric modeling

The first order conditional estimation with the interaction method was applied to the data. A PK/PD model was constructed in a sequential manner; first a sequential pharmacokinetic model for intravenously administered dexmedetomidine was built, followed by a mechanistic absorption model for subcutaneously administered dexmedetomidine. A pharmacodynamic model was built for noradrenaline/adrenaline concentration-time data alongside a fixed dexmedetomidine pharmacokinetic model. Finally, effect models for pharmacodynamic parameters (i.e. systolic and diastolic blood pressure, HR, vigilance and performance) were developed separately for each parameter with variable reserved data files. Inter-individual variability on the fixed effects parameters in the model was specified using an exponential model:

$$\Phi_i = \theta * e^{\eta_i}$$

where Φ_i represents the value of a fixed effect parameter for an individual, θ is the typical population value of the parameter, and η_i accounts for the inter-individual variability of the *i*th individual from the population typical value.

Inter-individual variability was introduced into all model parameters stepwise in nested models and accepted only if it led to a significant decline in the objective

function value (OFV), the ETA-shrinkage was <25%, and the model stability remained unaffected. In the pharmacokinetic model of dexmedetomidine with both administration routes, the residual variability in predicted concentrations was specified with a proportional error model:

$$C_{ij,x} = \hat{C}_{ij,x} * (1 + \varepsilon_{ij,x})$$

An additive error model was used for noradrenaline and adrenaline concentrations as well as for the remaining pharmacodynamic parameters,

$$C_{ij,x} = \hat{C}_{ij,x} + \varepsilon_{ij,x}$$

where x is one of the three substances, $C_{ij,x}$ is the *j*th observed concentration and $\hat{C}_{ij,x}$ is the model predicted concentration of the *i*th individual, and $\varepsilon_{ij,x}$ is a normally distributed random variable to quantify the residual variability in the concentrations. Both η and ε were assumed to be normally distributed random variables.

Among the nested models, the differences in the OFV were used to discriminate between models. A significance level of 0.05 equivalent to a decline of 3.84 points in the OFV was used. Model performance was evaluated with standard goodness-of-fit plots and prediction corrected visual predictive checks (Nguyen et al. 2017). Bootstrap analysis of the final models with 1000 replicates was carried out in order to calculate bias, standard errors and confidence intervals in the model parameters.

4.6. Analysis of pharmacodynamic effects

4.6.1 Assessment of hemodynamics effects

In Studies I and II, HR and in Study I, blood pressure was monitored continuously during follow-up and recorded at times of blood sampling. In Study III, HR was recorded continuously from the beginning to the end of the MRI procedure. In Study IV, HR was recorded continuously and MAP was measured at 5 min intervals from the beginning of the procedure until discharge from the PACU. HR and MAP were recorded before anesthesia induction, during wound incision, 1 h after anesthesia induction, during wound closure and in the PACU one hour after the operation.

4.6.2 Assessment of sedative effects

In Study I, psychomotor drug effects on vigilance and performance were assessed at times of blood sampling with a visual analogue scale (VAS). In Study II,

psychomotor drug effects on vigilance and performance were determined during blood sampling using a Comfort-B sedation scale (CBSS). The effect of dexmedetomidine on sedation was evaluated before administration of supplemental thiopental.

In Study III, the aim of sedation was to maintain the Modified Observer's Assessment of Alertness/Sedation Scale scores of the patients between 1 and 3, but the psychomotor drug effects of dexmedetomidine were not monitored. In Study IV, depth of sedation was monitored in the operation room using an entropy sensor (Entropy sensor; Datex-Ohmeda, Finland) to measure state entropy (SE) from frontal four-channel EEG. Effect site TCI concentrations of propofol and remifentanil, which all were recorded during wound incision, 1 hour after anesthesia induction and during wound closure.

4.6.3 Assessment of respiratory effects

Respiratory effects were monitored in all studies with pulse oximetry. In Study I, SpO_2 was monitored continuously for 10 h after administration of subcutaneous or intravenous dexmedetomidine, and in Study II, from administration of intranasal dexmedetomidine until at least one hour after MRI in all patients. SpO_2 was recorded in both studies at times of blood sampling.

In Study III, SpO_2 was monitored continuously during MRI. SpO_2 as well as oxygen delivery were obtained from the anesthesia report. Lowest and highest values of SpO_2 and use of (yes/no) supplemental oxygen administration were recorded. In Study IV, SpO_2 was monitored continuously from the beginning of the procedure until discharge of patients from the PACU, but SpO_2 was not included in the analysis of the study.

4.6.4 Assessment of sympatholytic effects

In Study I, plasma concentrations of adrenaline and noradrenaline were measured to assess the sympatholytic effects of dexmedetomidine. For adrenaline and noradrenaline concentrations, AUC was determined by using the trapezoidal rule in fractions of 0 to 0.5, 0 to 1, 0 to 2, 0 to 3 and 1 to 2 hours.

In Studies II and III, the sympatholytic effects of intranasally administered dexmedetomidine were determined by monitoring HR and by analyzing the decline of HR from the baseline in beats per minute and in percentages.

In Study IV, the sympatholytic effects of intranasally administered dexmedetomidine were assessed by monitoring HR and MAP from the beginning of the procedure until discharge from the PACU and comparing the hemodynamic parameters between the two groups.

4.6.5 Assessment of barbiturate- and opioid-sparing effects

In Study III, the requirement of thiopental during MRI was assessed retrospectively from the patient records. A 50% reduction in thiopental consumption was considered clinically significant. In Study IV, postoperative opioid consumption within 2, 12, 24, 36 and 48 h after the end of the surgery was assessed retrospectively from the patient records, converted to oral morphine equivalents (McPherson et al. 2010, Nielsen et al. 2016; Table 7) and compared between the two groups. A 15% reduction in postoperative opioid consumption was considered clinically significant.

Table 7. Opioid conversion table to oral morphine equivalents (1 mg to indicated mg of oral morphine).

Administration route	Per orally	Parenterally
fentanyl	-	300
oxycodone	1.5	3
pethidine	-	0.4
tramadol	0.2	-
codeine	0.1	-

Modified from McPherson et al. 2010 and Nielsen et al. 2016

4.7 Safety and adverse events

4.7.1 Assessment of local tolerability

In Study I, the local tolerability of subcutaneously and intravenously administered dexmedetomidine was assessed with VAS scores provided by the study participants immediately prior to drug administration (baseline) and at 1, 5, and 10 h. Subjective effects (no local pain/strong pain, no irritation/strong irritation, no pruritus/strong pruritus, no numbness/total numbness) were recorded. In the visual inspection by the investigator, possible signs of local dermal irritation, inflammation, bleeding and swelling were recorded.

In Study II, the local tolerability of intranasally administered dexmedetomidine was assessed by visual inspection by the investigator immediately prior to drug administration (baseline) and at 0.5 1, 2, and 4 h after administration of intranasal

dexmedetomidine. In the visual inspection conducted by the investigator, possible signs of local mucosal irritation, inflammation, bleeding and swelling were recorded.

4.7.2 Assessment of safety

In Studies I and II, the well-being of the study subjects was continuously monitored throughout the study sessions. Possible objective or subjective adverse events as well as concomitant treatments used to treat them were recorded in the case report form (CRF).

In Studies III and IV, possible objective or subjective adverse events as well as concomitant treatments used to treat them were collected from the hospital's patient information system and anesthesia reports, and possible adverse events (e.g. nausea and vomiting) related to the procedures were manually identified.

4.7.3 Reporting of Adverse Events (AE)

In Studies I and II, all AEs were documented and reported by the investigator from the moment of detection until the end of follow-up. All subjects were monitored at the study site for a minimum of 10 hours after drug administration in study I and for a minimum of 4 hours after drug administration in Study II. All AEs were recorded by the investigator in the appropriate space in the CRFs. AEs were detailed in CRFs according to the EMA guidelines.

In Studies III and IV, AEs were not documented or reported in real time, due to the retrospective nature of the studies. Unexpected difficulties during anesthesia had been recorded in the anesthesia report, which was evaluated for each patient. Possible AEs (eg. bradycardia or vomiting) related to the procedures were manually identified and reported.

4.8 Statistical analysis

4.8.1 Study hypotheses and outcomes

In Study I, our working hypothesis was that subcutaneously administered dexmedetomidine would be efficiently absorbed with attenuated sympatholytic effects compared to intravenous administration. The primary outcome variables determined in Study Ia were the observed concentrations of dexmedetomidine in plasma and its calculated pharmacokinetic parameters. The secondary variables were

HR, blood pressure, plasma adrenaline and noradrenaline concentrations, sedative effects, and possible local adverse effects.

In Study Ib, the aim was to build a PK/PD model that would account for the disposition kinetics of intravenous and subcutaneous dexmedetomidine, accurately describe the complex mechanism of dexmedetomidine absorption from the site of administration and mechanistically predict the effects of dexmedetomidine on HR, blood pressure as well as on subjective assessments of vigilance and performance.

In Study II, we hypothesized that intranasal doses of 2-3 µg/kg of dexmedetomidine would lead to the previously defined (i.e. 0.3-0.7 ng/ml) clinically effective plasma concentrations in children. The primary outcomes of the study were C_{max} and time to C_{max} (T_{max}). The secondary outcomes were area under the concentration-time curve ($AUC_{0\text{-}4h}$) and the pharmacological effects caused by single intranasal dexmedetomidine. The effect of age on dexmedetomidine pharmacokinetics was also evaluated.

In Study III, we hypothesised that intranasally administered dexmedetomidine (3 µg/kg) would markedly reduce the amount of additive barbiturate needed for MRI sedation. Our primary outcome was to compare the thiopental requirement after intranasal dexmedetomidine was added to the sedation protocol of pediatric patients undergoing MRI. Our secondary outcomes were to compare the lowest HR and SpO_2 values recorded, and the need for supplemental oxygen during the MRI.

The primary outcome of Study IV was postoperative opioid consumption in morphine dose equivalents. Perioperative MAP and HR were secondary outcomes. Our hypothesis was that intranasal administration of low doses of dexmedetomidine to supine anesthetized patients would exert beneficial effects on postoperative opioid consumption and hemodynamics.

4.8.2 Sample sizes

On the basis of previous studies (Iirola et al. 2011a, Scheinin et al 1992), it was calculated that 8 subjects would be needed for Study I to demonstrate a 30% difference in the AUC of plasma dexmedetomidine at a level of significance of $p = 0.05$ and power of 80%. To be prepared for drop-outs, we initially recruited 10 subjects and later recruited another replacement subject. For study II, we estimated that fifty pediatric patients would be sufficient based on similar pharmacokinetic studies conducted in children (Bradley et al. 2014, Chrysostomou et al. 2014, Nielsen et al. 2014).

The sample sizes of Studies III and IV were based on previous experience in similar retrospective studies (Gyanesh et al. 2014, Boriosi et al. 2017; Su et al. 2016, Ökmen et al. 2017). We evaluated the statistical power achievable with the planned sample sizes by calculating confidence intervals.

4.8.3 General statistics

The results are expressed as median (range or IQR), mean (standard deviation) or geometric mean (90% confidence intervals), depending on the distribution of the parameter. A qualified statistician chose and recommended specific tests for evaluating associations between the variables and differences between groups or treatments. In all studies, the data were evaluated for normality of distributions using probit plots and Shapiro–Wilk's W-test. Differences were regarded as significant at $p < 0.05$.

The data were analysed by using statistical programs in R language for Statistical Computing, version 3.3.2 (R Core Team 2017), in Rstudio, version 1.0.136 (RStudio Team 2016); R language for Statistical Computing, version 3.4.2; JMP Pro, version 13.0 for Mac (SAS Institute Inc., Cary, NC, USA) and SAS System programs, version 9.4. for Windows (SAS Institute Inc., Cary, NC, USA) in Studies I, II and III-IV, respectively. NONMEM 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA) was used for pharmacometric modeling.

4.8.4 Statistical inferences

In the pharmacokinetic Studies I and II, dexmedetomidine and catecholamine concentrations were log-transformed prior to computing pharmacokinetic parameters for each individual, but non-transformed results are reported. In Study II, concentrations were dose-corrected by the total dose before analysis.

In Study I, differences in pharmacokinetic variables were analysed using paired t-tests. Pharmacodynamic data were analysed using analysis of variance (ANOVA) for repeated measurements. Data were log-transformed before statistical analysis, but non-transformed results are reported.

In Study II, pharmacokinetic parameters and pharmacological effects were compared with one-way ANOVA, while T_{max} and the other time-related parameters were compared with the Kruskal-Wallis test. Levene's test for homogeneity of variances was used prior to ANOVA. The associations of dexmedetomidine concentrations in

plasma and the pharmacokinetic parameters with pharmacological effects were evaluated using Pearson's product moment correlation.

In Study III, primary outcomes were tested using the Kruskal-Wallis test and continued with age group comparisons (corrected with the Steel-Dwass method). Nominal data were tested using chi-square analysis.

In Study IV, a further subgroup analysis was performed between those patients receiving and not receiving NSAID therapy, by using the Kruskal-Wallis test and Wilcoxon's rank-sum test. Nominal data were tested using chi-square analysis.

V RESULTS

5.1 Non-compartmental pharmacokinetics of dexmedetomidine after subcutaneous administration

We included 8 subjects in the pharmacokinetic analysis of Study Ia, since two subjects were excluded before the intravenous phase, one for safety reasons and one for violation of the subject inclusion criteria. Median (range) T_{max} of dexmedetomidine was 15 (15-240) min after subcutaneous administration. The mean (range) bioavailability of subcutaneous dexmedetomidine was 81 (49-95)%. The mean (SD) C_{max} of dexmedetomidine in plasma was 0.3 (0.1) ng/ml (Figure 7). The pharmacokinetic results of Study Ia are summarized in Table 8.

Table 8. Pharmacokinetic parameters after 1 µg/kg doses of dexmedetomidine administered intravenously and subcutaneously to eight healthy volunteers.

Parameter	Intravenous	Subcutaneous	P
C_{max} (ng/ml)	2.4 (0.4)	0.3 (0.1)	< 0.001
T_{max} (h)	0.17 (0.08-0.17)	0.25 (0.25-4)	<0.001
$AUC_{0\text{-}10\ h}$ (ng min/l)	117 (20)	74 (21)	0.0019
$AUC_{0\text{-}\infty}$ (ng min/l)	121 (21)	109 (40)	0.328
CL/F (ml/min/kg)	-	903 (345)	-
V_z/F (l)	-	286 (81)	-
CL (ml/min/kg)	677 (109)	-	-
V_{ss} (l)	92.8 (9.9)	-	-
$t_{1/2}$ (min)	1.9 (0.3)	3.8 (0.9)	< 0.001
F (%)[a]	-	81 (49-97)	-

Data are shown as mean and SD, except for T_{max}, where median and range are shown.

[a] Statistical testing and bioavailability are based on data from those subjects who completed both treatment visits (n=8)

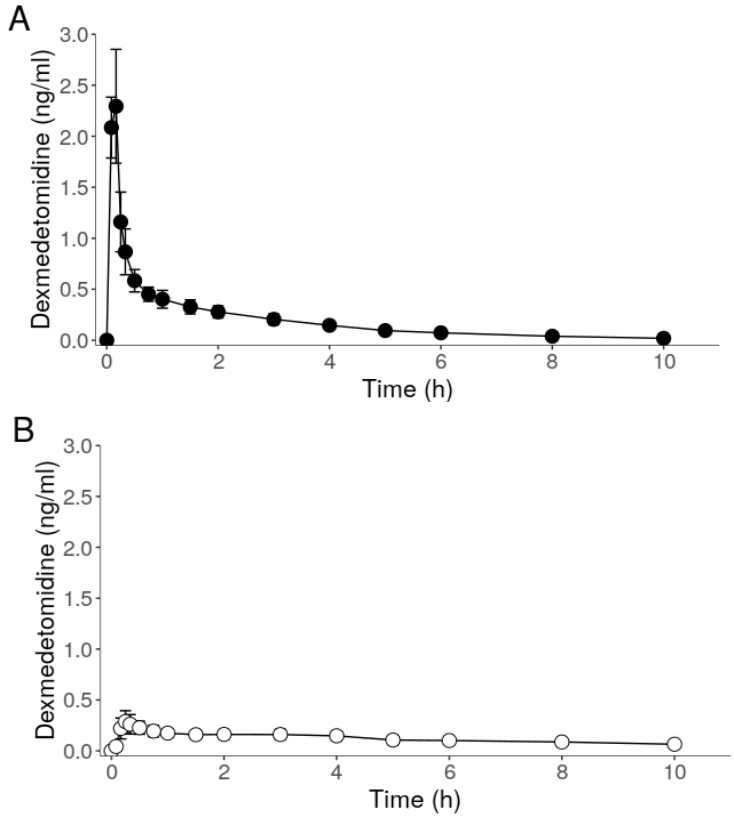

Figure 7. Mean (SD) plasma concentrations of dexmedetomidine after administration of 1 µg/kg of dexmedetomidine intravenously to eight (a) and subcutaneously to ten (b) healthy volunteers.

5.2 Pharmacometric modelling of subcutaneously administered dexmedetomidine

A semi-mechanistic structural model was developed. A two-compartment mammillary model proved to be better than a three-compartment model in explaining dexmedetomidine disposition kinetics [change in OFV = -331 and -346, respectively]. Plausible parameter estimates [CL_1 = 44.5 l/h, V_1 = 18.3 l, CL_2 = 115 l/h, V_2 = 77.6 l] and visual predictive checks described the model adequateness for depicting the data. In the second stage, the absorption of dexmedetomidine after subcutaneous administration was captured by the addition of a fat depot compartment. This assumption is supported by the high lipid solubility of dexmedetomidine. Rate constants for drug movement from this depot to the subcutaneous fat layer ($K_{a,FAT}$), from the depot to the central compartment ($K_{a,FAST}$) and from subcutaneous fat to the central compartment ($K_{a,SLOW}$) were estimated with adequate precision [$K_{a,FAT}$ = 3.11, $K_{a,FAST}$ = 1.11 and $K_{a,SLOW}$ = 0.13].

Next, indirect response models were employed to explain the dexmedetomidine-induced decreases in noradrenaline and adrenaline release. In the final stage models were built for subjective effects on vigilance and cognitive performance, as measured with visual analogue scales. E_{max} models with effect compartments were implemented and an additive model was used to estimate the effect of noradrenaline release as a surrogate measure of vigilance and performance as pharmacodynamic variables. Dexmedetomidine $EC50$ for causing 50 % inhibition of noradrenaline release was estimated at approximately 0.3 ng/mL, which is numerically close to the concentrations achieved in the study subjects with subcutaneous dosing of 1 µg/kg, and much lower than the drug concentrations achieved after intravenous dosing. All attempts to model epinephrine failed, indicating that the models were easily over-parametrised to provide a numerically stable predictive model output.

For blood pressure models, the net effect was coded as a sum of hyper- and hypotensive effects of dexmedetomidine due to vasoconstriction on peripheral arteries and sympatholysis mediated via the central nervous system. Reductions in blood pressure after dosing of dexmedetomidine were assumed to result from reduced noradrenaline concentrations in the noradrenaline release compartment, and a sigmoidal model with a biophase was utilised to estimate individual systolic and diastolic blood pressure values. Hypotensive effects of noradrenaline concentration fluctuations and hypertensive blood pressure effects due to plasma dexmedetomidine concentrations on systolic and diastolic blood pressure were defined in the model. A HR model combined the sympatholytic effect and other input from the central nervous system, predicted from arterial blood pressure levels. We added an inhibitory effect of systolic blood pressure on HR, mediated by baroreceptor reflex activation in the central nervous system, to account for the misfit in the HR model, which resulted in an unbiased output. We hypothesized, that HR reductions after dexmedetomidine administration included an effect component that is dependent on the blood pressure levels and mediated by the baroreceptor reflex. Model-predicted systolic blood pressure estimates from our final blood pressure model were used to drive an indirect response model for HR regulation. Subjective effects of dexmedetomidine were coded using a biophase and sigmoidal direct effect models.

5.3 Pharmacokinetics of dexmedetomidine after intranasal administration in pediatric patients

Data from 50 patients were analysed in Study II. The mean (SD) dose-corrected C_{max} was 0.011 $litre^{-1}$ (0.0051) and the median interquartile range (IQR) T_{max} was 37 (30-45) min. We found significant negative associations between dose-corrected C_{max} and subject age [Pearson's r = -0.58; 95% confidence interval (CI) -0.74 – -0.37, $p < 0.001$] and dose-

corrected $AUC_{0\text{-}4\,h}$ versus age (r = -0.53, 95% CI -0.70 – -0.29; p < 0.001). T_{max} did not correlate with age (r = -0.14; 95% CI -0.14 - 0.39; p = 0.35) (Figure 8 and Table 9).

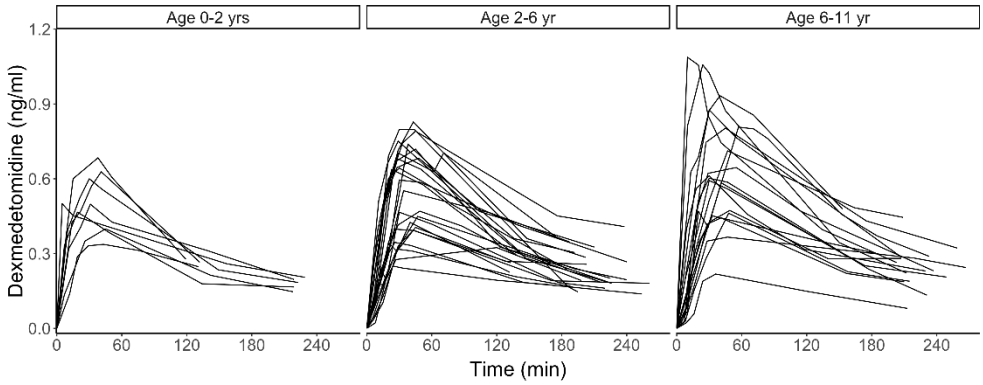

Figure 8. Individual concentration-time curves after intranasal 3 µg/kg dosing of dexmedetomidine as a nasal spray in three age groups of children.

Table 9. Dose-corrected pharmacokinetic parameters of dexmedetomidine after administration of 2-3 µg kg^{-1} doses as nasal spray to 50 ambulatory pediatric patients.

Parameter	All patients	Age 0-2 yr	Age 2-6 yr	Age 6-11 yr	P
C_{max} (ng/ml)	0.54 (0.17)	0.46 (0.11)	0.51 (0.17)	0.61 (0.18)	-
C_{max}/D (1/litre)	0.011 (0.0051)	0.016 (0.0048)	0.011 (0.0046)	0.0086 (0.0040)	< 0.001
T_{max} (min)	37 (30 – 45)	35 (22 – 43)	32 (28 – 45)	41 (30 – 47)	0.52
$AUC_{0\text{-}4}$ (ng/min/ml)	68 (23)	61 (21)	69 (25)	77 (21)	-
$AUC_{0\text{-}4}$ /D (min/ml)	1.40 (0.61)	1.90 (0.51)	1.42 (0.66)	1.14 (0.45)	0.0035

Data are shown as mean and SD, except for T_{max}, where median and IQR are shown. D, dose (µg) of dexmedetomidine

5.4 Barbiturate and opioid sparing effects of intranasal dexmedetomidine

5.4.1 Barbiturate sparing effect

In Study III, 200 patients were included in the analysis. Significantly smaller induction and total doses of thiopental were needed for completion of the planned MRI procedure in all dexmedetomidine groups as compared to the corresponding control group. The difference was statistically significant in all three clinically relevant age groups. The median (IQR) cumulative thiopental requirement during MRI was 4.4 (2.7–6.0) mg/kg/h

compared to 12.4 (9.8– 14.8) mg/kg/h in the dexmedetomidine and control groups, respectively (median difference 7.9 mg/kg/h, 95% CI: 6.8–8.8, P < 0.001).

The median (IQR) induction doses of thiopental before MRI were 1.8 (1.2–2.3) mg/kg in the dexmedetomidine treated children, almost three times lower than the value in the control group, 5.1 (4.6–6.2) mg/kg (median difference 3.3 mg/kg/h, 95% CI: 3.1–3.6, P < 0.001) (Figure 9).

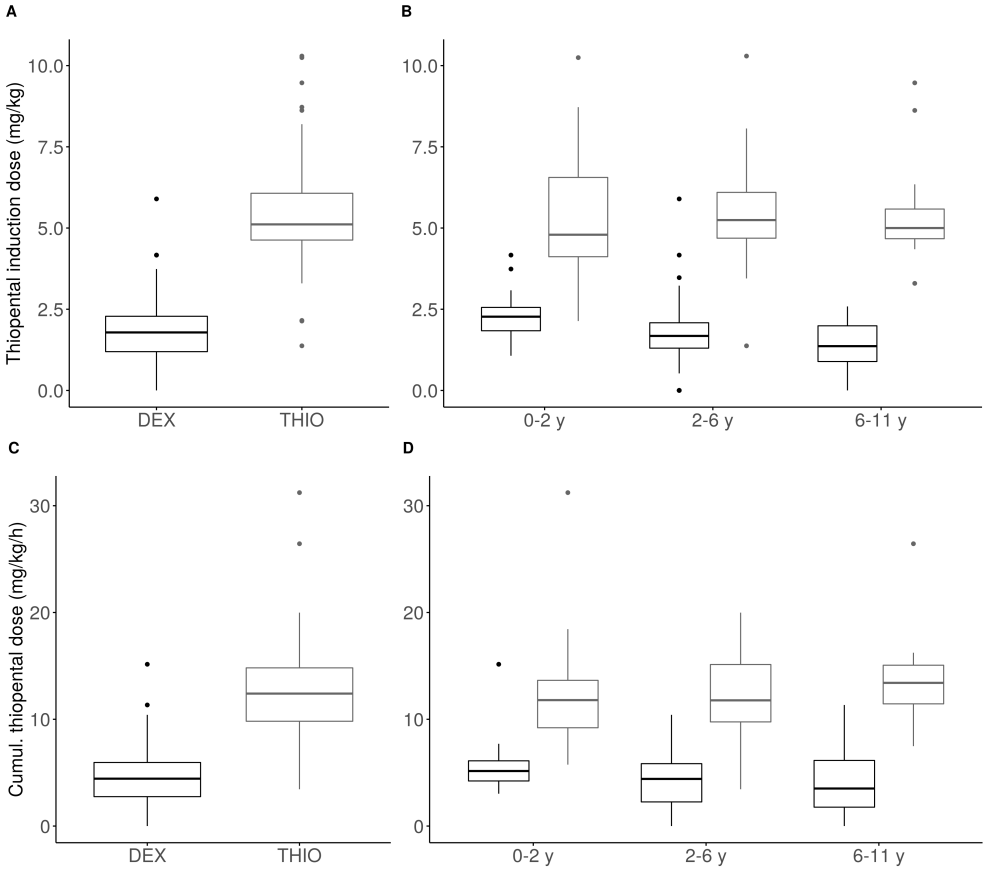

Figure 9. Box plots showing the difference in induction doses (mg/kg) of thiopental between the dexmedetomidine and thiopental groups (A) and in the three clinically significant age groups after dexmedetomidine + thiopental or only thiopental (B). Below, the cumulative doses of thiopental (mg/kg/h) are shown for the dexmedetomidine and thiopental groups (C) and for the three clinically significant age groups (D).

5.4.2 Opioid sparing effect

In Study IV, 120 patients were included in the analysis. The cumulative postoperative opioid requirement (in oral morphine equivalents) was significantly less in the

dexmedetomidine group as compared to the control group (26.3 mg, 95% CI 15.6 to 36.4, P < 0.001). The cumulative dose was significantly different between the groups at 12, 24 and 36 h postoperatively (p = 0.01; p = 0.001; p < 0.001) (Figure 10).

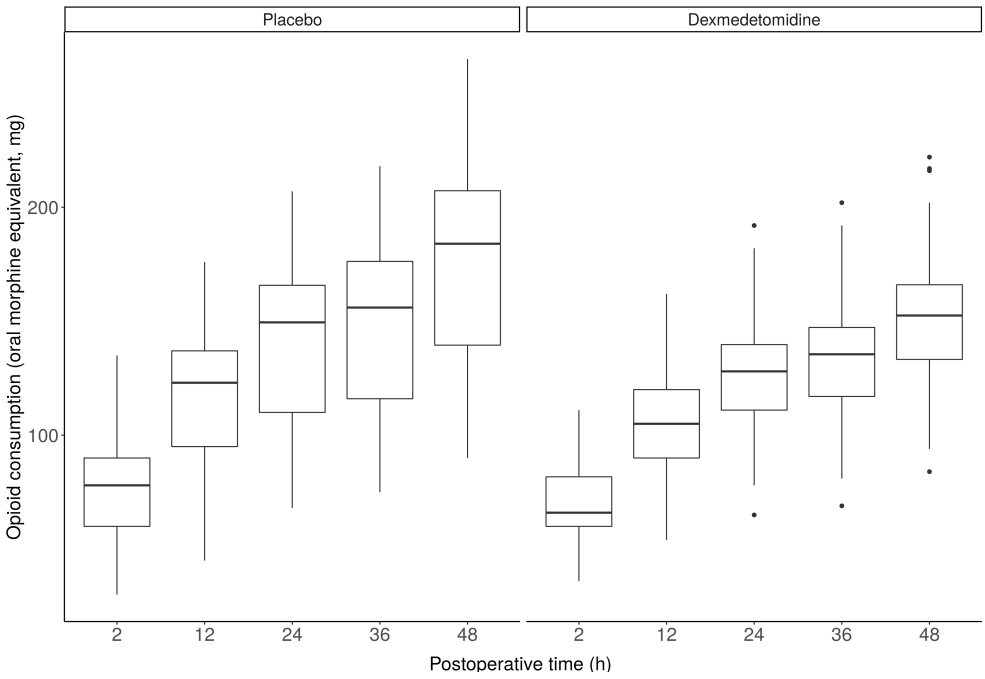

Figure 10. Box plots showing the cumulative postoperative opioid requirement in the control and dexmedetomidine groups. Results are reported as oral morphine equivalent doses within 2, 12, 24, 36 and 48 h of surgery.

5.5 Hemodynamic and sympatholytic effects

5.5.1 Hemodynamic effects

Compared to subcutaneous dosing, mean MAP was significantly lower during 0–120 min (P < 0.032) after intravenous administration of dexmedetomidine in Study I. HR decreased initially after intravenous dosing, but there were no statistically significant differences between the two administration routes when maximum decreases or epochs over 0–30 or 0–60 min after drug administration were tested.

In Study II, the mean (SD) decrease in HR after dexmedetomidine dosing was 16 (8.9) bpm and the lowest mean (SD) HRs before administration of supplemental thiopental in the three age groups were 95 (11), 76 (13) and 69 (10) bpm, respectively (Figure 11).

In Study III, the mean (SD) of the lowest measured HR was 78 (16) bpm in the dexmedetomidine group compared to 92 (12) bpm in the thiopental group (P < 0.001) (Figure 11). Blood pressure was not routinely recorded in the subjects of this study.

In Study IV, the HR and MAP of the dexmedetomidine group were lower compared to the control group in the PACU (P = 0.008; P < 0.001). The dexmedetomidine group had higher MAP values intraoperatively (P < 0.001), but also used more intraoperative vasoactive medication (P = 0.01). There was no difference in intraoperative bleeding between the two groups (P = 0.86).

5.4.2 Effects on catecholamines

In Study I, plasma noradrenaline concentrations remained significantly smaller (P < 0.001) after intravenous than subcutaneous dexmedetomidine during the entire sampling period, 3 h after dosing, and the calculated noradrenaline $AUC_{0–180\ min}$ was significantly smaller (P < 0.001) after intravenous than after subcutaneous dexmedetomidine (Figure 12). Plasma adrenaline concentrations were significantly lower for the first 60 min after intravenous drug administration (P = 0.037), but after that time point, there were no significant differences between the treatments.

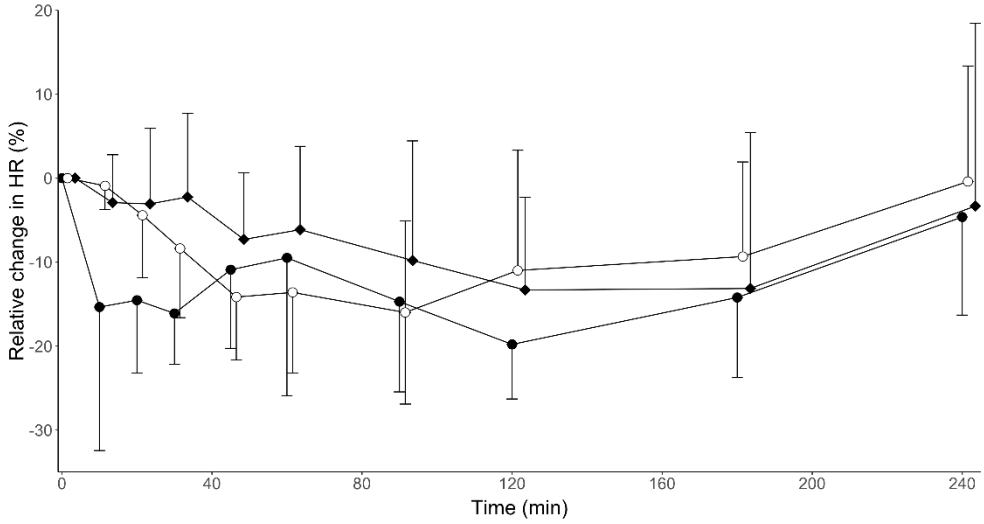

Figure 11. Relative change in heart rate (%) after administration of 1 ug/kg of intravenous dexmedetomidine (•) or subcutaneous dexmedetomidine (♦) to healthy volunteers or 2-3 ug/kg of intranasal dexmedetomidine to pediatric patients* (o).

*patients received additional thiopental for sedation 60 min after administration of dexmedetomidine

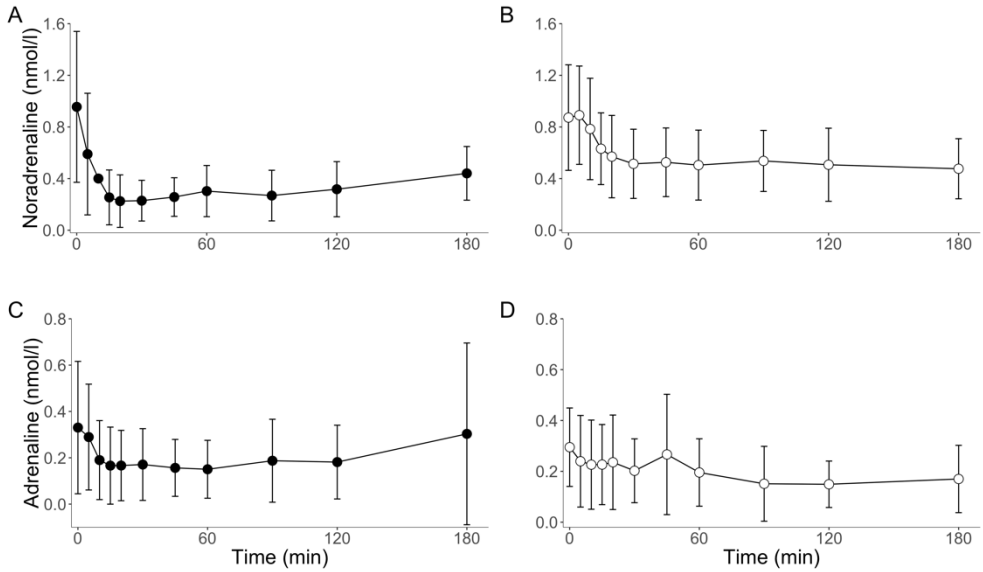

Figure 12. Mean (SD) adrenaline and noradrenaline concentrations in plasma after administration of 1 µg/kg of dexmedetomidine intravenously (●) to eight and subcutaneously (o) to ten healthy male volunteers.

5.5 Sedative effects

Subjective effects of dexmedetomidine on vigilance in Study I are shown in Figure 13. The scores for vigilance were significantly lower at 0–60 min after intravenous injection than after subcutaneous dosing ($P < 0.001$), but at later time points, the subjects tended to be more sedated after subcutaneous than after intravenous administration. Concentrations of dexmedetomidine in plasma usually associated with sedative effects (i.e., > 0.2 ng/ml) were present for 4 h in both groups (Figure 13).

In Study II, maximal sedation after administration of intranasal dexmedetomidine was achieved in 45 min. The median (IQR) decrease in CBSS was 8 (6-9) points from the baseline (Figure 13). Dexmedetomidine concentrations in plasma > 0.2 ng/ml were achieved in all patients. However, 47 patients required additional sedation to achieve the completion of the MRI procedure and thus were dosed with thiopental. The median (IQR) thiopental dose was 2.6 (1.6-5.1) mg/kg; the median times to thiopental administration were 68 min, 66 min and 86 min in the three age categories, respectively. In Study III, depth of sedation was not recorded.

In Study IV, depth of sedation was monitored intraoperatively with SE, which was recorded at three different time points. There were no statistically significant

differences at any time point between the dexmedetomidine and control groups. There was also no statistically significant difference in PACU time between the groups.

5.6 Respiratory effects

In Study I, SpO_2 remained unchanged in all patients. In Study II, SpO_2 remained clinically acceptable in all patients after administration of dexmedetomidine. Immediately after the thiopental administration, one patient received supplemental oxygen since his SpO_2 value decreased to 91%.

In Study III, thirty-three (33%) of the patients in the control group received supplemental oxygen whereas only two (2%) of the dexmedetomidine group patients needed oxygen ($P < 0.001$). Despite the less frequent oxygen administration in the dexmedetomidine group, the lowest observed peripheral oxygen saturation reading was higher in these patients as compared to the control group ($P < 0.001$). In Study IV, there was no difference in the frequency of oxygen administration between the two groups ($p = 0.63$).

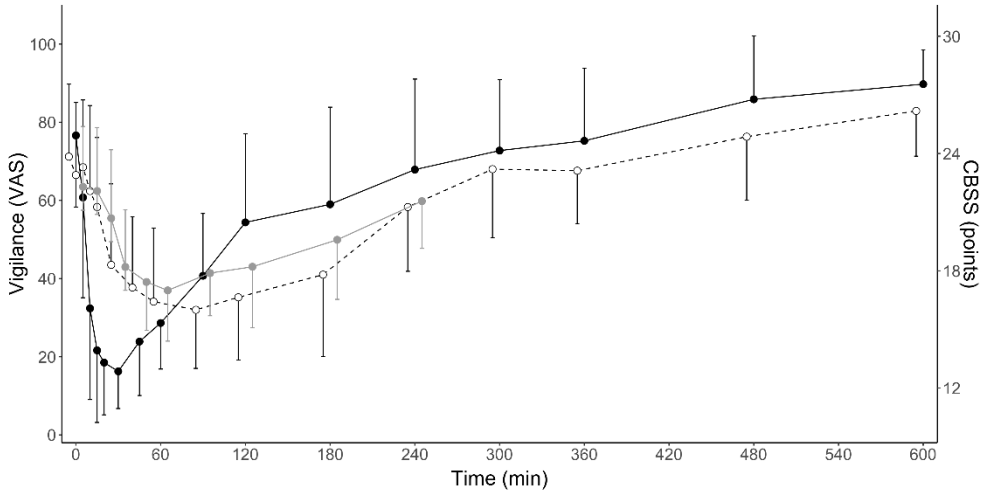

Figure 13. Sedative effects of dexmedetomidine after intravenous (●) or subcutaneous (o) administration of 1 ug/kg to healthy volunteers and after intranasal (●) administration of 2-3 ug/kg of dexmedetomidine to pediatric patients*. Left y-axis represents VAS scale for vigilance (Study I) and right y-axis represents CBSS scores (Study II).

*the patients received additional thiopental for sedation at 60 min after administration of dexmedetomidine

5.7 Safety and tolerability

One subject was withdrawn from Study I for safety reasons after the subcutaneous administration phase due to emergence of bradycardia between 32 to 39 bpm at 1 h after drug administration; this symptom resolved after 4 h without interventions and was not associated with subjective symptoms.

In Studies II and III, two patients (aged 4.7 and 7.8 years) received atropine for bradycardia (36 and 39 bpm, respectively) soon after receiving thiopental one hour after administration of 3 μg/kg intranasal dexmedetomidine.

In Study II, one patient receiving 2 μg/kg of intranasal dexmedetomidine and 5 mg/kg of intravenous thiopental vomited after the MRI procedure. In Study III, two patients in the dexmedetomidine group and two patients in the control group reported mild nausea after MRI but no vomiting was recorded.

In Study II, the reported adverse events were mild and mostly related to an unpleasant feeling in the nasal mucosa (3 out of 50 children) immediately after administration of the nasal spray. Nasal irritation was not observed in nor reported by any of the patients, but crying was observed in sixteen (32%) patients and a runny nose occurred in eight (16%) patients. In Study III, local irritation was not reported. In Study IV, no adverse events were recorded.

VI DISCUSSION

6.1 Methodological aspects

6.1.1 Study I

A randomized, controlled and balanced study design was used. A cross-over design was chosen in order to reduce the effect of inter-individual variation. The cross-over design also helped to keep the number of volunteers small as each subject served as his own control. In order to further reduce inter-individual variability, we recruited young, normal-weight healthy male volunteers. Only eight subjects received intravenous dexmedetomidine; this is the reason why we decided to include only 8 subjects in the analysis of Study Ia. Data from all subjects were included in the analysis of Study Ib.

Dexmedetomidine dosing was based on the product label information and corresponded with the dosages that have been previously suggested for palliative sedation (Kent et al. 2005, Soares et al 2002). It would have been interesting to study bolus dosing of subcutaneously administered dexmedetomidine, but since intravenous bolus dosing is not recommended, we chose to apply the same administration rate in both treatments in order to maintain comparability.

We collected plasma samples for concentration measurements of dexmedetomidine for 10 h and for concentration measurements of catecholamines for 3 h. Despite this relatively long sampling period, the fraction of extrapolated $AUC_{0-\infty}$ was 28% in the subcutaneous phase. It would have been more informative to collect blood samples over a longer period. Similarly, measurement of catecholamines could have been longer, since both adrenaline and noradrenaline concentrations still appeared to be declining 180 min after drug administration. However, any differences in the adrenaline and noradrenaline responses between the two administration routes were probably most likely to be evident already during the first hour after drug administration.

A wash-out period of 3 weeks was utilized to minimize the risk of possible carry-over effects. Pre-dose blood samples were drawn for controlling possible carry-over in the second study session, but none of the pre-dose samples of the study subjects exceeded the lower limit of dexmedetomidine quantification.

Study Ib was a PK/PD modeling study based on the subject population of Study Ia, except that all 10 subjects were included in the analysis. Modelling of the absorption

of dexmedetomidine from subcutaneous injection site proved to be challenging. Several attempts to model topical dexmedetomidine absorption, including first order absorption, single Weibull absorption and biphasic absorption with slow absorption ($K_{a,\ slow}$), did not yield satisfying models. Thus, a biphasic fat compartment model with fast absorption ($K_{a,\ fast}$) and slow absorption ($K_{a,slow}$) processes was devised and a fat layer permeation constant (K_{fat}) was used. This model described the movement of dexmedetomidine into a subcutaneous fat layer and from there to the circulation. Our model was able to capture the dexmedetomidine, noradrenaline and adrenaline concentration-time profiles and pharmacodynamic effects quite well. Compared to intravenous administration, the HR decreases were less pronounced after subcutaneous dexmedetomidine while the central nervous system effects (as reflected by drowsiness) were more pronounced.

Although our pharmacometric model captured the data well and the model can be utilized in simulation studies, it should be emphasized it is solely based on data from healthy volunteer subjects. In addition, only a short dexmedetomidine infusion was employed.

6.1.2 Study II

Our main objective was to evaluate drug absorption after intranasal dosing. We decided to recruit pediatric patients with a wide age range, but recruitment of the youngest age group (1 month to 2 years) proved to be challenging due to the small number of such patients actually requiring sedation for MRI. This resulted in an uneven distribution of patients in the three clinically relevant age groups. The timing of the blood sampling was not perfect for a non-compartmental analysis, but we were able to obtain over 300 blood samples from 50 pediatric patients, which is more than in earlier similar pharmacokinetic studies conducted in children (Bradley et al. 2014, Chrysostomou et al. 2014, Nielsen et al. 2014). Experimental PK/PD modeling will be performed for the same patient population in the future.

Based on earlier observations in healthy adult volunteers (Iirola et al. 2011a), we drew two samples during the assumed absorption phase, two samples during the distribution phase and two samples to cover the elimination phase. It would have been more informative to collect further blood samples, but as our patients were discharged after four hours, further follow-up and blood sampling was not possible. Despite such a relatively short sampling period, we were able to capture informative concentration-time profiles for each patient.

The administration of dexmedetomidine as a nasal spray has been investigated mainly in preoperative applications with a dosing range of 0.5 to 2 µg/kg (Yuen et al. 2008, Talon et al. 2009, Cimen et al. 2013). We wanted to study higher doses based on previous reports where up to 9 µg/kg/h doses of intravenous dexmedetomidine have been used for pediatric patients undergoing MRI (Mason et al. 2010, Siddappa et al. 2011). At the time when our study was initiated, there was no prior pharmacokinetic information about intranasal dexmedetomidine in children.

The dose volumes of delivered intranasal dexmedetomidine varied from 240 µl to 1200 µl, which by far exceeds the volumes usually considered as ideal. Although the largest doses were divided into both nostrils, the used volumes were still two to six times larger than those employed in commercial nasal spray products (Djupesland et al. 2013). This may have affected intranasal drug absorption negatively, and calls for the development of a drug product with a higher concentration of dexmedetomidine, or improved drug delivery systems compared to the one used in this study, if intranasal application is to be clinically applicable.

The Ramsey Sedation Scale and Richmond Agitation and Sedation Scale are commonly employed for monitoring the depth of sedation in ambulatory pediatric patients. We chose to use the CBSS to assess the depth of sedation as this scale is routinely used in our pediatric ICU. The use of the CBSS does not need any verbal or physical stimulation, which can be considered an advantage in pediatric patients that are breathing spontaneously and are expected to lie motionless. Sedation with dexmedetomidine at doses of 2-3 µg/kg was considered clinically acceptable as decreases of 6 or more points in the CBSS have been suggested to indicate a good response to sedative agents in pediatric patients (Boerlage et al 2015).

6.1.3 Study III

We compared retrospectively two different pediatric MRI sedation protocols. Our hypothesis was that intranasally delivered dexmedetomidine would decrease the requirement of intravenous thiopental. We also hypothesized that the risk of respiratory depression caused by thiopental would be reduced when intranasal dexmedetomidine was used as premedication.

The number of patients included in the study was sufficient, since the observed differences in thiopental consumption were highly significant in all three age categories. Considering respiratory depression evoked by thiopental, it would have been more informative to measure the respiratory rate and end tidal CO_2 with nasal capnography. Although respiratory rate was not reported, SpO_2 recordings during

MRI sedation were significantly higher in the dexmedetomidine group, in spite of the higher frequency of supplemental oxygen administration in the control group.

We measured sympatholytic effects caused by dexmedetomidine premedication by recording HR. It would have been more informative to investigate also blood pressure during the MRI in both groups, but this was not possible since blood pressure was not routinely measured in the MRI unit. However, the effect of intranasally administered dexmedetomidine on the blood pressure of pediatric patients has been previously evaluated and doses of 3 µg/kg have not been found to cause clinically significant hypotension or hypoperfusion (Li et al 2015). Furthermore, the incidence of hypertension has been low when higher doses of dexmedetomidine have been given intravenously to pediatric patients undergoing MRI (Mason et al 2010).

6.1.4 Study IV

Study IV was a retrospective analysis seeking to correlate the use of intranasally administered dexmedetomidine with opioid use after total hip replacement surgery. We included healthy ASA 1-2 patients with body weight between 50 and 100 kg in order to maintain the dosage of intranasal dexmedetomidine between 0.5 and 1.0 µg/kg and in order to avoid confounders related to comorbidity. All patients received total intravenous anesthesia (TIVA), which has been associated with excellent recovery in outpatient surgery (Bruderer et al. 2017). However, the use of remifentanil as an anesthetic agent may carry a risk for hyperalgesia (de Hoogd et al. 2016), and multimodal management of anesthesia and analgesia in patients undergoing total hip arthroplasty under TIVA has been considered warranted (Stevenson et al. 2018).

All patients in our study received perioperatively oral paracetamol, local anesthetic infiltration around the hip joint and intravenous betamethasone, which all have been shown to reduce postoperative opioid consumption compared to placebo in patients undergoing total hip arthroplasty (Hickman et al 2018, Murphy et al. 2012, Fan et al. 2018). Our results suggest that the use of intraoperative low-dose dexmedetomidine significantly reduced postoperative opioid consumption compared to the control group, despite the concomitant administration of other analgesic adjuvants. Although in patients undergoing total hip arthroplasty, concomitant NSAIDs can ease postoperative pain as compared to placebo (Zhou et al. 2001), NSAIDs were not given to all patients because of various contraindications (e.g. asthma). A *post hoc* subgroup analysis showed a statistically significant

difference in the postoperative opioid consumption between the two groups also when NSAID use was taken into account.

We included fentanyl administration in the analysis of the primary endpoint, but since all study patients received 100 μg of intravenous fentanyl after termination of the TIVA, administration of fentanyl could well have been removed from the analysis of postoperative opioid consumption. This would have increased the difference in postoperative opioid consumption between the two groups.

6.2 Pharmacokinetics of dexmedetomidine after subcutaneous administration

The pharmacokinetics of extravascularly administered dexmedetomidine has mostly been studied in healthy volunteer subjects (Dyck et al. 1993a, Anttila et al. 2003, Iirola et al. 2011a). Our current findings suggest that dexmedetomidine has a similar bioavailability after subcutaneous, intranasal, and intramuscular administration and confirm that its bioavailability is sufficient for clinical efficacy also after subcutaneous administration.

The bioavailability of subcutaneous dosing was 36% smaller during the sampling period ($AUC_{0–10\ h}$) when compared to intravenous dosing. When AUC was extrapolated to infinity ($AUC_{0–\infty}$), the mean bioavailability of subcutaneously administered dexmedetomidine was 81%. The pharmacokinetic parameters determined for intravenous dexmedetomidine were in line with earlier reports (Dyck et al 1993b).

Previous studies have shown that intravenous administration of dexmedetomidine evokes dose-dependent decreases in HR and MAP, concomitantly with decreases in plasma catecholamines. However, initial hypertension may occur with high plasma concentrations related to a rapid administration of dexmedetomidine (Kallio et al 1989, Ebert et al 2000, Snapir et al 2006). The hemodynamic, sedative and sympatholytic effects of subcutaneously administered dexmedetomidine emerged significantly more slowly when compared with intravenous administration. In order to diminish dexmedetomidine-induced hypertension and bradycardia after intravenous dosing, we used 10-min constant-rate infusions with both administration routes. Intravenous dosing did not result in hypertension, but significant decreases were seen in HR and blood pressure. Compared to this, subcutaneous administration was associated with smaller reductions in HR and MAP, which may reduce the risk of hemodynamic depression compared to intravenous dosing.

Subcutaneous dosing resulted in lower peak plasma concentrations compared to intravenous administration, but similar plasma concentrations were measured 3 h after dexmedetomidine dosing during both study phases. In accordance, the onset of sedation was delayed after subcutaneous dexmedetomidine compared to intravenous administration. Although there were no statistically significant differences in the duration of the sedative and hemodynamic drug effects between the two administration routes, the effects appeared to be reversed slightly more slowly after subcutaneously dosing compared to intravenous administration.

Pronounced inhibition of sympathetic nervous system activity was reflected by reduced plasma noradrenaline concentrations after intravenous administration of dexmedetomidine. The onset of this effect was less abrupt and the reductions were smaller after subcutaneously injected dexmedetomidine.

Study Ib aimed to create a PK/PD model that would describe the absorption of dexmedetomidine from the subcutaneous site of dosing. The mechanism-based PK/PD model of subcutaneously administered dexmedetomidine had several unique features. Dexmedetomidine has an octanol/buffer partition coefficient of 2.8, which allows entrance of the drug into fat tissue and slows its systemic absorption. A biphasic absorption model was therefore devised such that a fast absorption process was responsible for the influx of drug from the subcutaneous depot into the systemic circulation and a fat layer permeation constant was introduced to depict drug movement into the subcutaneous fat layer. A slow absorption process described the zero-order drug release from the subcutaneous fat layer. Although the scenario represents a biphasic absorption process, no strict criterion was coded into the model to describe the temporal shift between the two processes, and these were modelled simultaneously.

The pharmacodynamic endpoints of HR and systolic and diastolic blood pressure are to some extent dependent on the biological concentrations of noradrenaline and adrenaline. However, due to the lack of a validated adrenaline model, these pharmacodynamic variables were assumed to be functions of noradrenaline concentrations only. The noradrenaline concentrations at the release compartment were used as the key determinant of the HR and systolic/diastolic blood pressure effect. In spite of these limitations, we could implement a combination of both hypertensive and hypotensive effects into our model for blood pressure. Finally, to model subjective effects, we assumed that the apparent noradrenaline concentrations at the release (synaptic) compartments were driving these with no other contributing mechanisms. Compared to intravenous administration, the HR decreases were less affected after subcutaneous dexmedetomidine while the central nervous system

effects (as reflected by drowsiness) were more sensitive. The output from the final model exhibits adequate model performance, plausible model parameter estimates with low relative standard error values, and a reasonable model fit as demonstrated by the standard GOF plots and visual predictive checks. Although our pharmacometric model captured the data well and we believe that the model can be utilized in simulation studies, it is emphasized that it is solely based on data from healthy volunteers. In addition, only a short dexmedetomidine infusion was employed.

6.3 Pharmacokinetics of intranasal dexmedetomidine in pediatric patients

Intranasal dexmedetomidine was rapidly absorbed in pediatric patients and C_{max} was achieved in a median time of 37 min. There was, however, extensive inter-individual variability between study subjects, as previously reported in healthy adult volunteers (Iirola et al. 2011a, Li et al. 2018). One main reason for the inter-individual variability may be inadequate absorption of the drug related to unsuccessful drug administration and/or the large dosing volumes. The youngest age group (0-2 yr) had significantly higher dose-adjusted values of C_{max} and drug exposure ($AUC_{0\text{-}4\ h}$) compared to the older patients. Peak concentrations might even continue to decrease with age, since the dose-corrected C_{max} calculated for adult healthy volunteers (Iirola et al 2011a) was smaller (0.0060) than that now found in the oldest age group of our study (0.0086). This correlation of C_{max} with age may be linked to the larger dosing volumes needed in the older subjects.

A recent study (Miller et al. 2018) evaluated the pharmacokinetics of intranasal dexmedetomidine in twelve pediatric patients (age 6-44 mo) undergoing cardiopulmonary bypass. Half of the patients received 1 µg/kg and the others received 2 µg/kg of intranasal dexmedetomidine. Median C_{max} of dexmedetomidine was 0.2 and 0.36 ng/ml and median T_{max} was 47 and 46 min after the two different dosages. In our study, the mean C_{max} (0.54 ng/ml after a mean dose of 2.8 µg/kg) was similar to previous findings, but time to peak concentration was slightly shorter. There was, however, high variability in T_{max}. Moreover, the patients examined by Miller et al. had congenital heart disease and were anesthetized and supine during administration of intranasal dexmedetomidine, which could all have affected the disposition of dexmedetomidine (Miller et al. 2018).

We hypothesized that intranasal doses of 2-3 µg/kg of dexmedetomidine would lead to clinically efficacious plasma concentrations in children. Some previous studies have indicated that dexmedetomidine plasma concentrations between 0.3 and 0.8

ng/ml are required to provide mild to moderate sedation in pediatric patients and adults, respectively (Potts et al. 2009, Ebert et al. 2000, Yoo et al. 2015). The mean C_{max} in our study was 0.54 ng/ml, suggesting that sedative concentrations are achieved after intranasal 2-3 µg/kg doses of dexmedetomidine. However, almost all patients required additional sedation with thiopental. Moreover, concentration-time profiles indicated that the plasma concentrations of dexmedetomidine decrease quite rapidly, which suggests that higher initial doses or repeated dosing may be needed for clinical efficacy for longer procedures.

Our findings suggest that there was no difference in the sedative effects of dexmedetomidine between the different age groups. The average decline in CBSS was 8 points from the baseline and maximal reductions were recorded 45 min after dosing in all three age categories. This can be considered as clinically acceptable sedation, as decreases of 6 or more CBSS points have been demonstrated to represent a good response to sedative agents in pediatric patients (Boerlage et al. 2015).

Based on the present and some previous findings, the optimal dose of intranasal dexmedetomidine for ambulatory sedation of pediatric patients may be at least 3 µg/kg (Mekitarian Filho et al. 2015, Baier et al. 2016). Our results indicate that dexmedetomidine concentrations in plasma declined relatively rapidly also after intranasal dosing. Higher doses may be needed to prolong the sedative effect. On the other hand, the time to discharge might then be prolonged, and further studies will be needed in order to define the optimal dosing of intranasal dexmedetomidine. Intranasally administered dexmedetomidine as the sole agent might not be sufficient for MRI sedation of pediatric patients, and combinations with other sedative agents, mainly $GABA_A$ receptor modulators, may be needed.

6.4 Barbiturate sparing effect of intranasally administered dexmedetomidine

Some previous studies have retrospectively evaluated the effect of dexmedetomidine on propofol consumption in pediatric MRI sedation (Boriosi et al. 2017, Nagoshi et al. 2018), but as far as we are aware, this is the first study to have investigated the impact of premedication with intranasally administered dexmedetomidine on barbiturate (thiopental) requirements for procedural MRI sedation of children. In previous studies, pediatric patients were sedated for MRI with intravenous propofol with or without 0.5-2 µg/kg doses of intravenous dexmedetomidine. In both studies, the use of dexmedetomidine as part of the sedation regimen reduced propofol consumption and airway complications compared to the control group.

Our results suggest that significantly less thiopental is needed for sedation of children for MRI when intranasal dexmedetomidine is used as premedication. Before the use of intranasal dexmedetomidine, supplemental oxygen has had to be provided to a significant number of patients. Considering the fact that thiopental may cause respiratory depression and other adverse effects, then a substantially reduced consumption of thiopental is considered to be beneficial and may reduce the risk of adverse events in MRI sedation of children. Even though 33% of the control group patients (but only 2% of the dexmedetomidine patients) received supplemental oxygen, peripheral blood oxygen saturation was lower in the control group. This suggests that the use of intranasal dexmedetomidine as premedication may protect patients from the hypercapnia and respiratory depression sometimes evoked by oxygen administration.

Almost all (98%) of the patients in the dexmedetomidine group received thiopental due to emergence and anxiety during transfer from their hospital bed to the MRI room. To reduce the need of additional sedation after intranasal dexmedetomidine, it might be worthwhile to wait until the patient falls asleep again on the MRI bed. The use of two sedative agents with two different mechanisms of action for sedation in pediatric patients undergoing MRI appears to represent a safe protocol with respect to preserving adequate respiration and maintaining hemodynamic control. The use of intranasal dexmedetomidine as premedication does not, however, appear to totally eliminate the need for $GABA_A$ receptor modulators.

6.5 Opioid sparing effect of intranasally administered dexmedetomidine

Study IV demonstrated that intraoperatively administered intranasal low-dose dexmedetomidine reduced opioid requirement in patients undergoing total hip arthroplasty. Previously, the use of intravenous dexmedetomidine as intraoperative adjunct has been shown to reduce postoperative pain and opioid consumption in orthopedic surgical procedures (Kim et al. 2017, Shin et al. 2018), but the intranasal administration route of dexmedetomidine has never been investigated in this patient population.

The rationale for the intraoperative use of extravascular dexmedetomidine instead of intravenous dosing is to avoid the latter's adverse hemodynamic effects (Iirola et al. 2011a). Perioperative administration of intranasal dexmedetomidine has been mostly studied in pediatric patients and only a few studies on adult patients have been conducted. In these previous studies, the employed dose of intranasal

dexmedetomidine was higher (1.5-2.0 μg/kg) than in our study (Nooh et al. 2013, Lu et al. 2016, Qiao et al. 2016).

In previous studies in patients undergoing total hip arthroplasty, clinically meaningful morphine-sparing effects of other analgesic adjuvants have been considered to be 10-15 mg of intravenous morphine over 48 h postoperatively (Kardash et al. 2008). Thus, the difference found in our study (26 mg of oral morphine) may be considered as clinically significant.

The anesthetic sparing effect of dexmedetomidine may be reflected in entropy (Iirola et al. 2011, Kim et al. 2017). We used relatively low doses of intranasal dexmedetomidine, which did not have statistically significant effects on intraoperative SE levels. However, the use of intraoperative vasoactive medication was higher in the dexmedetomidine group, suggesting that there may be a slightly lower need for intraoperative administration of propofol and remifentanil after administration of intranasal dexmedetomidine.

We included relatively healthy adult patients in our study and were not able to monitor postoperative delirium, but it would be interesting to examine whether intranasally administered low-dose dexmedetomidine could exert a beneficial impact on postoperative delirium in elderly and cognitively impaired patients undergoing total hip arthroplasty.

Our study revealed that use of intranasal low-dose dexmedetomidine as an intraoperative adjunct in supine anesthetized patients undergoing total hip arthroplasty has clinically significant effects on postoperative opioid consumption, accompanied by rather minor hemodynamic side effects. Postoperative opioid consumption is a common concern of all care providers. An appreciation of the benefits of opioid sparing techniques and multimodal analgesia will help physicians to improve postoperative pain management.

6.6 Hemodynamic and sympatholytic effects of dexmedetomidine

Dexmedetomidine has effects on HR and blood pressure, which is probably the main reason restricting its use outside of operation rooms and ICUs. Many studies have shown that dexmedetomidine causes individually variable, biphasic responses in blood pressure as well as the decrease in HR due to its vasoconstrictive and sympatholytic effects. The best known side effect of dexmedetomidine is bradycardia, and previous studies have indicated that dexmedetomidine decreases HR by 15-20% from the baseline (Ebert et al 2000, Mason and Lerman 2011). We

observed similar decreases in HR in all studies, but in most cases, the decreases in HR did not require any interventions. In Studies III and IV, the use of dexmedetomidine was compared to a control group and statistically significant differences were observed in HR, but with no clinically significant impact on patient care.

Especially in pediatric patients, reductions in HR may cause concern, since cardiac output of newborns and infants has been traditionally considered to be HR dependent (Mason and Lönnqvist 2015). However, already three decades ago it was demonstrated that even newborns are capable of increasing their cardiac output by augmenting their stroke volume (Vinberg and Lundell 1990). The HR slowing effect of dexmedetomidine is actually very similar to natural sleep, which has been observed to reduce HR by 15-20% from awake levels (Montague et al. 1982, Fleming et al. 2011). In view of the fact that dexmedetomidine induces a kind of drug-induced sedation mimicking natural sleep, the reductions in HR may be considered, at least partly, physiological. Although combined with thiopental administration, our results in Studies II and III showed that intranasal use of 2-3 μg/kg doses of dexmedetomidine decreased HR on the average by 16 bpm (by 8.9%). In both studies, HR was reduced most in our youngest patients (0-2 years of age). Despite the rather small reductions in HR in our studies, safety trials regarding the intranasal use of dexmedetomidine are lacking, and HR as well as signs of hypoperfusion should be closely monitored when administering dexmedetomidine to infants.

In Study I, a dose of 1 μg/kg dexmedetomidine administered either subcutaneously or intravenously did not cause any signs of hypotension or hypoperfusion in the healthy volunteer subjects. The subjects were, however, kept in a supine position for at least 4 hours after dexmedetomidine dosing and we cannot rule out that dexmedetomidine-induced sympatholysis could have triggered orthostatic reactions. Thus, it is safer to keep patients in the supine position for at least the duration of the drug's sedative effects.

We observed significantly lower MAP in Study I at 0-120 min after intravenous dosing compared to subcutaneous dosing. This coincided with plasma noradrenaline concentrations that remained significantly lower during the entire sampling period after intravenous compared to subcutaneous administration. Considering the possible use of subcutaneous administration in palliative care, where hemodynamic monitoring may be challenging or lacking, these findings are favourable.

In Study IV, we observed lower postoperative HR and MAP in the dexmedetomidine group, suggesting that the hemodynamic effects of intranasally administered

dexmedetomidine are significant even at doses of 0.5-1.0 μg/kg. Compared to the control group, there was no difference in PACU time. Furthermore, hemodynamic parameters remained clinically acceptable and no vasoactive treatments were needed in the postoperative care of the dexmedetomidine-treated patients. Together with its analgesic effect, the sympatholytic properties of dexmedetomidine may help to reduce perioperative bleeding and may be beneficial for patients with ischemic heart disease. On the other hand, the reduced MAP as compared to the control group could impair diuresis. Since dexmedetomidine has also diuresis enhancing properties, it would have been interesting to compare urine output between the groups, but since the patients undergoing total hip arthroplasty had not been implanted with urinary catheters, we were not able to assess diuresis.

6.7 Sedative effects of dexmedetomidine

In Study I, the subjective scores for vigilance and performance were significantly lower at 0-60 min if the drug had been injected intravenously in comparison with its subcutaneous dosing. At later time points, the subjects tended to be more sedated after subcutaneous administration, but the difference was not statistically significant.

The sedative effects of intranasal administration of dexmedetomidine in children undergoing surgery have already been documented by others. Our findings regarding the sedative effects of intranasal dexmedetomidine in Studies II and III are similar to previous results published for pediatric patients (Kim et al. 2017). Our results suggest that the use of intranasal dexmedetomidine in pediatric patients for MRI sedation is a useful adjuvant modality in this patient population, but might not alone be sufficient for procedural MRI sedation of pediatric patients. Sedation with dexmedetomidine resembles physiological sleep and maintains the patient in an arousable state, which may actually be problematic in procedures where the patient is expected to remain immobile. Patients sedated for MRI should, however, be arousable soon after the procedure so that they can be discharged from the imaging unit. Thus, the use of dexmedetomidine as part of sedation appears reasonable. Determining the optimal dose, drug concentration and the drug delivery system for intranasal dexmedetomidine dosing are topics for future investigations.

Dexmedetomidine has analgesic and amnestic effects and it has been shown that its use as an anesthetic adjunct has similar effects as propofol on the bispectral index and entropy (Patel et al. 2012). In Study IV, the sedative effects of dexmedetomidine were monitored with SE, but no statistically significant differences in SE levels or in the need for other anesthetics were observed in comparison to the control group.

There was, however, a tendency to lower SE levels and to reduce the need for propofol and remifentanil in the dexmedetomidine group. Probably, the use of larger doses of dexmedetomidine as an anesthetic adjunct would emphasize the difference. In order to avoid intraoperative awareness, monitoring of the depth of sedation with entropy or with the bispectral index is warranted when dexmedetomidine is used as a general anesthesia adjunct.

6.8 Safety of extravascularly administered dexmedetomidine

In Study I, one participant experienced asymptomatic bradycardia of 32–39 bpm, which emerged 60 min after subcutaneous administration of dexmedetomidine. He was a tall athlete with a low resting HR of 40–42 bpm. The results of previous studies indicate that dexmedetomidine causes significant cardiac conduction effects via depression of the sinoatrial node, thus decreasing resting HR by up to 15–20% (Ebert et al. 2000). Even if the change in HR was not unexpected, we decided to exclude this subject from the intravenous administration phase to avoid the risk of severe bradycardia. In spite of the observed bradycardia, the blood pressure of the excluded subject remained acceptable. The other nine subjects exhibited no significant adverse effects.

In Studies II and III, two patients receiving intranasal dexmedetomidine displayed significant bradycardia soon after dosing of intravenous thiopental. Although previous studies indicate that active correction of bradycardia in pediatric patients after dexmedetomidine dosing may cause hypertension (Subramanyam et al. 2015), our patient was given atropine to increase the HR. We observed no serious adverse effects related to bradycardia or with the combined dosing of dexmedetomidine and atropine. Dexmedetomidine was well tolerated and only transient adverse effects were recorded. Intranasal doses were easy to deliver to the patients, and drug administration was always accomplished. No bleeding or local irritation was observed or reported by the patients. These findings suggest that the intranasal route may be a safe mode of dexmedetomidine administration.

In Study IV, the employed dexmedetomidine dose was relatively low and dexmedetomidine was not expected to cause any hemodynamic or other adverse effects. Although when used as an intraoperative adjunct, dexmedetomidine may cause prolonged postoperative sedation, intranasal doses of 0.5-1.0 μg/kg did not have any effects on the PACU time as compared to the control group.

6.9 Limitations of the studies

The limitations to Studies I and II include the short sampling period for dexmedetomidine plasma samples, since dexmedetomidine concentrations remained high in both studies after extravascular dosing. Study I included only healthy young male volunteers. The main limitation of Study II is the lack of complete standardization in the dosing regimens. The administration of thiopental was at the discretion of the attending anesthesiologist. The sampling time was only 4 hours and a total of 6 blood samples were collected during this time, whereas in Study I sixteen samples were collected over 10 hours. It would have been more informative to collect further blood samples in both studies to determine dexmedetomidine elimination after subcutaneous and intranasal administration.

To evaluate the sympatholytic effects caused by dexmedetomine more precisely, it would have been beneficial to monitor blood pressure in Studies II and III. Since a patient sedated with dexmedetomidine is easily arousable, non-invasive blood pressure monitoring with cuff inflation may awaken the patient and therefore we were not able to routinely measure blood pressure in the pediatric patients undergoing MRI procedures.

The retrospective design of Studies III and IV could have affected the results, even though consecutive patients were systematically collected in order to avoid any selection bias. A relatively new sedation protocol was used in both studies at the time when the patients in the dexmedetomidine group were treated and protocol was changed during the study. This might have influenced the outcomes as the personnel sedating children for MRI and the personnel treating patients undergoing total hip arthroplasty were still collecting experience on the use of intranasal dexmedetomidine. On the other hand, only a very limited numbers of anesthesiologists and other staff were in charge of all of the patients in Studies III and IV.

The dose of dexmedetomidine used in Study IV was relatively small, which may have limited its effects, especially with respect to secondary outcomes. Intranasal dexmedetomidine was administered to supine patients, which could have affected drug absorption. However, a recent published pharmacokinetic study conducted in anesthetized pediatric patients undergoing heart surgery and receiving intranasal dexmedetomidine in the supine position, reported that the drug's relative bioavailability was 84% (Miller et al. 2018).

6.10 Ethical considerations

The aims of our prospective studies – to characterize the pharmacokinetics, bioavailability, sedative effects and local tolerability of subcutaneously and intranasally administered dexmedetomidine in healthy volunteers and in pediatric patients, respectively – were scientifically sound and ethically justified. The investigators were aware of the ethical issues and risks associated with the study procedures.

The doses of dexmedetomidine employed in Studies I-IV were based on previous studies and were not considered to exert any marked effects on respiration and blood oxygen saturation. Small transient decreases in blood pressure and simultaneous decreases in HR were expected when dexmedetomidine was administered, especially intravenously.

In Study I, the hemodynamic effects were assessed as being non-symptomatic but the subjects were kept in semi-recumbent position during the first 3 hours after dexmedetomidine administration. A qualified physician experienced in anesthesiology was present during the study sessions and monitored continuously the safety and clinical well-being of the subjects. The study procedures included cannulation of a vein and an artery, which were not considered to constitute a significant health hazard to the subjects. A total volume of less than 300 ml of blood was drawn from each subject during the study sessions.

In Study II, the patients received intranasal dexmedetomidine and underwent venous cannulation as part of their care, regardless of whether or not the patient was participating in the study. Blood sampling was not considered to constitute a significant health hazard to the patients, since an amount less than 1% of total blood volume was drawn from each patient during the study for plasma dexmedetomidine analysis. A qualified physician experienced in pediatric anesthesiology was present during the study sessions and monitored the safety and well-being of the patients. The patients were only discharged after they were assessed as being fit for safe discharge in the investigator's opinion. All patients and their guardians were appropriately informed of the discomforts and possible risks associated with this study and were free to withdraw their consent at any time without loss of health care or other benefits. Studies III-IV were retrospective studies that did not have any impact on patient care. Relatively new treatments were studied in both studies, which is ethically justified and may increase the safety of patient care.

6.11 Future studies

The pharmacodynamic effects of extravascularly administered dexmedetomidine have been studied earlier with several administration routes and with various dosages. Our studies mainly focused on intranasal administration, which appears to be the most popular route. Intranasal administration of dexmedetomidine is off-label, but its use is becoming increasingly popular as a premedication and intraoperative adjunct. Subcutaneous administration of dexmedetomidine is relatively new and more studies are warranted to clarify its pros and cons.

A drug solution with a higher dexmedetomidine concentration would be beneficial regarding extravascular dosing. Only one injectable formulation of dexmedetomidine is commercially available (100 µg/ml), and the dosing volumes often exceed the recommended volumes for intranasal administration. It should be further investigated whether doses greater than 3 µg/kg have similar bioavailabilities as doses of 1 and 2 µg/kg. It would also be interesting to study the concentration of dexmedetomidine in cerebrospinal fluid, since it has been claimed that intranasal drug administration may allow direct absorption of the drug into the central nervous system (Khan et al. 2017).

Subcutaneous administration of sedative and analgesic drugs has been widely used in palliative care (Thomas et al. 2015). The slow onset of effects after subcutaneous administration of dexmedetomidine could be beneficial by providing prolonged sedation for patients in palliative care, obviating the need for intravenous administration. Our results suggest that subcutaneous administration of dexmedetomidine could be a useful addition to the armament of drugs used for palliative sedation. Analgesic and opioid-sparing effects of dexmedetomidine may be beneficial for palliative care patients with opioid hyperalgesia. Furthermore, dexmedetomidine may reduce the likelihood of delirium, at least when compared to sedation with propofol or benzodiazepines. However, we investigated healthy volunteers, and no placebo control session was included in the study. Only a few case reports regarding the use of dexmedetomidine in palliative care have been published (Hilliard et al. 2015, O´Hara et al. 2015), and it should be further investigated whether subcutaneously administered dexmedetomidine is a feasible way to sedate patients in end-of-life care. Although our results may encourage the use of subcutaneous administration of dexmedetomidine, our findings should be considered as preliminary, and further trials are warranted. Furthermore, dexmedetomidine pharmacokinetics after continuous or model-informed subcutaneous infusions should be evaluated.

Intranasal administration of dexmedetomidine is off-label use, as in fact is all kind of use of this drug in pediatric patients. Due to the feasibility, safety and ease of administration of intranasal dexmedetomidine, its use is increasing as a premedication and as an intraoperative adjunct. A recent retrospective study evaluated the usefulness of an intranasally administered dexmedetomidine-ketamine combination in sedation of more than 16 000 pediatric patients undergoing MRI. The sedation protocol was found to be associated with acceptable efficacy and low rates of adverse events (Yang et al. 2019). The combination of dexmedetomidine and ketamine appears to be a promising way to treat anxiety and pain in both pediatric and adult patients. Both drugs have good bioavailabilities after intranasal administration. Clearly, further studies on the use of dexmedetomidine-ketamine combinations are warranted.

VII SUMMARY AND CONCLUSIONS

The results of the clinical investigations presented in this thesis give rise to the following conclusions:

1. The average bioavailability of subcutaneously administered dexmedetomidine was good (81%), but the interindividual variation was large. Subcutaneously administered dexmedetomidine was efficacious and well tolerated. For patients requiring light sedation, subcutaneous administration of dexmedetomidine may be a feasible alternative, since this route was associated with attenuated sympatholysis as compared to intravenous administration. According to our results, subcutaneous dexmedetomidine should be administered 60-90 min prior to the desired maximal effect.

2. The pharmacometric model developed for subcutaneously dosed dexmedetomidine indicates that the local fat compartment might slow down drug absorption from the subcutaneous site of injection. Even if the pharmacodynamic effects of dexmedetomidine are more subtle after subcutaneous dosing, further model-based studies will be needed to evaluate the clinical significance of this finding.

3. Our results demonstrated that intranasally administered dexmedetomidine at doses of 2-3 μg/kg was relatively rapidly absorbed and achieved acceptable sedation in pediatric patients requiring ambulatory sedation. Intranasal dexmedetomidine exhibited rather similar properties in pediatric patients as encountered in adults, but peak concentrations and exposure to the drug appeared to decrease with age. Further studies on the optimal dosage and delivery methods of intranasal dexmedetomidine for procedural MRI sedation appear warranted.

4. Intranasal dexmedetomidine markedly reduced the requirement of thiopental in ambulatory sedation of pediatric patients. Compared to sedation with thiopental alone, the use of intranasal dexmedetomidine as premedication attenuates sympathoadrenal stress responses, does not compromise respiration, and has an excellent recovery profile in MRI sedation of pediatric patients.

5. Intranasal dexmedetomidine administered in doses as low as 0.5-1.0 μg/kg decreased postoperative opioid consumption in adult patients undergoing total hip arthroplasty. Our results represent a basis for further clarification of the dose-response of intranasal dexmedetomidine with respect to postoperative analgesia in surgical patients.

VIII ACKNOWLEDGEMENTS

This study was carried out in the Perioperative, Intensive Care and Pain Management Services, Turku University Hospital, and the Department of Anesthesiology and Intensive Care, University of Turku, Finland during the years 2015-2019. I wish to express my sincere gratitude to:

Associate professor Teijo Saari, MD, PhD, for his inspiring supervision of this study and for being very approachable during its most demanding years. His enthusiastic guidance and broad knowledge of anesthetic pharmacology have made this journey easier to travel. I have felt privileged to have been given an opportunity to work under his supervision.

Professor Emeritus Mika Scheinin, MD, PhD, for his inspirational supervision of this study. This project would not have been possible without his extensive knowledge of pharmacology and especially about α2-agonists. I truly admire his knowledge and expertise in dexmedetomidine research.

The late Professor Riku Aantaa, MD, PhD, for inspiring me when I started research into dexmedetomidine and for teaching me so much about dexmedetomidine and pediatric anesthesiology. In addition to being a respected academic and anesthesiologist, he was also a brilliant person. He will always be remembered and missed.

Adjunct Professor Tuula Manner, MD, PhD, our head of department, for introducing me to this project already in the year 2011, for her interest and support and for her valuable contribution and efforts along the way.

My co-authors Muhammad Ashraf, MSc, Samuel Guillaume, MD, Henrik Jätinvuori, MD, Jussi Kosola, MD, PhD, Eliisa Löyttyniemi, MSc, Mirjam Lehtinen, MD, Saija Siren, MSc, Ida Tilli, MD and Sanna Vilo, MD, for helping me during this thesis project.

Adjunct Professor Kaj Kiviluoma, MD, PhD and Professor Mikko O. Niemi, MD, PhD, for being the official referees of this thesis and for their instructive reviewing and constructive criticisms. Ewen MacDonald, Pharm.D. for prompt English revision of this thesis.

Adjunct Professor Anu Maksimow, MD, PhD and Juha Lähde, MD, my current bosses for their support and for allowing me to take time off from my routine work to complete this research project.

All healthy adult volunteers, all adult patients and especially all of the brave children who participated in these studies. Adjunct Professor Leena Kainulainen, MD, PhD,

for being helpful when initiating the studies on pediatric patients. Matti Helkiö, MD for allowing me to conduct studies in the operative unit of Salo Regional Hospital. All of the nurses from the Pediatric Operation Unit and Pediatric Day Hospital of Turku University Hospital, for helping with the recruitment process of pediatric patients. Elina Kahra, BLS for her invaluable help in the laboratory.

All of my colleagues in the Department of Anesthesiology and Intensive Care for their friendship and support at our daily work. The list is very long but I must mention a few - I am especially grateful to my colleagues Petri A, Riku A, Ulla A, Ari A, Juha G, Ville-Veikko H, Lauri L, Mikael L, Antti L, Monna M, Marko P, Pirkka R, Urmas S, Annalotta S, Markku T and Marika V for always being supportive with regard to this thesis project. Secretaries Henna I and Maarit K are acknowledged for invaluable help in the practical matters.

I am fortunate in having many great friends and I wish to acknowledge you all. Special thanks to Akseli, Hannes, Joni, Matias, Mikael, Petri, Saku, Tuukka, Valtter, Veikko and Vili for all the good moments together.

My mother Elina for the beautiful cover painting of this book and for her endless love, help and support that I have received throughout all of these years, my sisters Anni and Rita and their husbands Asmo and Mikko for being supportive and loving friends to me and my father Jorma for his love and support. My nephews, Akseli, Lauri and Onni, and my niece, Isla for bringing bundles of joy into my life. My late aunt, Silja for always supporting me. My parents in law, Jaana and Juha and my grandma-in-law Aila for being so willing to help us whenever needed.

Finally, I want to express my gratitude to my fiancé, Anna-Leena for her love and support and especially for being a loving mom to our son. Eino brings a smile to my face every day and has made me realize what is most important in life. I dedicate this work to both of you, with love.

This work was financially supported by Turku University Foundation, by TYKS Foundation, by the Pediatric Cancer Foundation, by the Emil Aaltonen Foundation, by the Finnish Culture Foundation and Government's Special Financial Transfer tied to academic research in Health Sciences (Finland).

Turku September 2019

Panu Uusalo

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UNIVERSITY OF TURKU

Painosalama Oy, Turku , Finland 2019

ISBN 978-951-29-7774-1 (PRINT)
ISBN 978-951-29-7775-8 (PDF)
ISSN 0355-9483 (PRINT) ISSN 2343-3213 (ONLINE)