TURUN YLIOPISTON JULKAISUJA
ANNALES UNIVERSITATIS TURKUENSIS

SARJA - SER. D OSA - TOM. 1004

MEDICA - ODONTOLOGICA

OBSERVATIONS ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF DEXMEDETOMIDINE

Clinical Studies on Healthy Volunteers and Intensive Care Patients

by

Timo Iirola

TURUN YLIOPISTO
UNIVERSITY OF TURKU
Turku 2012

Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
University of Turku and Turku University Hospital, Turku, Finland

Department of Pharmacology, Drug Development and Therapeutics,
University of Turku, and TYKSLAB, Unit of Clinical Pharmacology, Turku, Finland

Supervised by

Professor Klaus Olkkola, M.D., Ph.D.
Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
University of Turku and Turku University Hospital, Turku, Finland

Docent Riku Aantaa, M.D., Ph.D.
Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
University of Turku and Turku University Hospital, Turku, Finland

Docent Erkki Kentala, M.D., Ph.D.
Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine
University of Turku and Turku University Hospital, Turku, Finland

Reviewed by

Docent Anne Kuitunen, M.D., Ph.D.
Department of Anesthesiology, Intensive Care, Emergency Care and Pain Medicine
Helsinki University Hospital, Helsinki, Finland

Docent Minna Tallgren, M.D., Ph.D.
Department of Anesthesiology, Intensive Care, Emergency Care and Pain Medicine
Helsinki University Hospital, Helsinki, Finland

Opponent

Professor Esko Ruokonen, M.D., Ph.D.
Department of Intensive Care
University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

ISBN 978-951-29-4906-9 (PRINT)
ISBN 978-951-29-4907-6 (PDF)
ISSN 0355-9483
Painosalama Oy – Turku, Finland 2012

To Karoliina, Pyry and Aura

ABSTRACT

Timo Iirola

OBSERVATIONS ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF DEXMEDETOMIDINE

Clinical Studies on Healthy Volunteers and Intensive Care Patients

Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Turku and Turku University Hospital, Turku, Finland
Department of Pharmacology, Drug Development and Therapeutics, University of Turku, and TYKSLAB, Unit of Clinical Pharmacology, Turku, Finland

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2012

Patients treated in intensive care units require sedation and analgesia. However, sedative drugs also have potential adverse effects, and there is no single ideal sedative-analgesic drug for these patients.

Dexmedetomidine is an α_2-adrenoceptor agonist licenced for sedation of intensive care patients and patients undergoing surgery and other invasive procedures. Several routes of parenteral administration (intravenous, intramuscular, subcutaneous and intranasal) have been utilized.

In the present series of studies, the pharmacokinetics and pharmacodynamics of intranasally administered dexmedetomidine as well as the gastrointestinal effects of intravenous dexmedetomidine were determined in healthy volunteers. Pharmacokinetics of dexmedetomidine during long lasting, high-dose infusions were characterized in intensive care patients.

The bioavailability of intranasal dexmedetomidine was relatively good (65%), but interindividual variation was large. Dexmedetomidine significantly inhibited gastric emptying and gastrointestinal transit. In intensive care patients, the elimination half-life of dexmedetomidine was somewhat longer than reported for infusions of shorter duration and in less ill patients or healthy volunteers. Dexmedetomidine appeared to have linear pharmacokinetics up to the studied dose rate of 2.5 μg/kg/h. Dexmedetomidine clearance was decreasing with age and its volume of distribution was increased in hypoalbuminaemic patients, resulting in a longer elimination half-life and context-sensitive half-time.

Intranasally administered dexmedetomidine was efficacious and well tolerated, making it appropriate for clinical situations requiring light sedation. The clinical significance of the gastrointestinal inhibitory effects of dexmedetomidine should be further evaluated in intensive care patients. The possibility of potentially altered potency and effect duration should be taken into account when administering dexmedetomidine to elderly or hypoalbuminaemic patients.

Keywords: dexmedetomidine, intensive care, pharmacokinetics, pharmacodynamics

TIIVISTELMÄ

Timo Iirola

HAVAINTOJA DEKSMEDETOMIDIININ FARMAKOKINETIIKASTA JA FARMAKODYNAMIIKASTA

Kliininen tutkimus terveillä vapaaehtoisilla ja tehohoitopotilailla

Anestesiologian, tehohoidon, ensihoidon ja kivunhoidon klinikka, Turun yliopisto ja Turun yliopistollinen keskussairaala, Turku
Farmakologia, lääkekehitys ja lääkehoito, Turun yliopisto ja TYKSLAB, Kliinisen farmakologian yksikkö, Turku

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, 2012

Tehohoitopotilaat tarvitsevat rauhoitusta ja kivunlievitystä. Kuitenkin rauhoittavilla lääkkeillä on myös haitallisia vaikutuksia, eikä yksittäistä ideaalista lääkettä näiden potilaiden lääkitsemiseksi ole olemassa.

Deksmedetomidiini on tehohoito- ja toimenpidepotilaiden rauhoittamiseen rekisteröity α_2-adrenoseptoreja aktivoiva lääkeaine. Sitä on käytetty suonensisäisesti, lihaksensisäisesti, ihonalaisesti ja nenän limakalvolle annosteltuna.

Tässä tutkimussarjassa tutkittiin nenän limakalvolle annostellun deksmedetomidiinin farmakokinetiikkaa ja farmakodynamiikkaa sekä suonensisäisesti annostellun deksmedetomidiinin vaikutuksia mahalaukun ja suoliston toimintaan terveillä vapaaehtoisilla koehenkilöillä. Deksmedetomidiinin farmakokinetiikkaa tutkittiin suuriannoksisen ja pitkäkestoisen annostelun aikana tehohoitopotilailla.

Nenän limakalvolle annostellun deksmedetomidiinin hyötyosuus oli melko hyvä (65%), mutta yksilöiden välinen vaihtelu oli laaja. Deksmedetomidiini hidasti maha-suolikanavan toimintaa merkittävästi. Tehohoitopotilailla deksmedetomidiinin puoliintumisaika oli hieman pidempi kuin lyhytaikaisemman käytön jälkeen ja parempikuntoisilla potilailla tai terveillä vapaaehtoisilla. Deksmedetomidiinin farmakokinetiikka vaikutti lineaariselta tutkitulle annostasolle 2,5 µg/kg/h saakka. Deksmedetomidiinin puhdistuma oli pienentynyt ikääntyneillä potilailla ja jakautumistilavuus kasvanut hypoalbumineemisilla potilailla, minkä seurauksena eliminaatiovaiheen puoliintumisaika ja annostelun kestosta riippuva puoliaika pitenivät.

Nenänsisäisesti annosteltu deksmedetomidiini oli tehokasta ja hyvin siedettyä, minkä vuoksi se sopii lievää rauhoittamista vaativiin tilanteisiin. Mahasuolikanavaan kohdistuvan vaikutuksen kliininen merkitys pitää tutkia tehohoitopotilailla. Annosteltaessa deksmedetomidiinia ikääntyneille tai hypoalbumineemisille potilaille pitää varautua vaikutuksen poikkeukselliseen voimakkuuteen ja kestoon.

Avainsanat: deksmedetomidiini, tehohoito, farmakokinetiikka, farmakodynamiikka

TABLE OF CONTENTS

ABBREVIATIONS

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUEC_{0-t}$	area under effect-time curve from time zero to t hours
BIS	bispectral index
BMI	body mass index
cAMP	cyclic adenosine 3,5-monophosphate
Cl	plasma clearance
Cl_{dial}	haemodiafiltration clearance
Cl_{ss}	plasma clearance at steady state
Cl_1	systemic clearance
Cl_2	rapid distributional clearance
Cl_3	slow distributional clearance
C_{max}	peak plasma concentration
CO	cardiac output
C_{ss}	concentration at steady state
CV	coefficient of variation
CYP	cytochrome P450
F	bioavailability
FiO_2	fraction of inspired oxygen
GABA	γ-aminobutyric acid
GFR	glomerular filtration rate
G-protein	guanine nucleotide binding protein
ICU	intensive care unit
I_{ss}	infusion rate at steady state
k_e	elimination rate constant
MAP	mean arterial pressure
MDAPE	median absolute prediction error
MDPE	median prediction error
OFV	objective function value
PaO_2	partial pressure of oxygen in arterial blood
Q	inter-compartmental clearance
RASS	Richmond Agitation Sedation Scale
RCO	normalized measured cardiac output
SAPS II	Simplified Acute Physiology Score II
SE	standard error (of the mean)
SD	standard deviation
SpO_2	arterial oxyhemoglobin saturation measured by pulse oximetry
$t_{1/2}$	elimination half-life in a one-compartment model
$t_{1/2\alpha}$	distribution half-life in a two-compartment model
$t_{1/2\beta}$	elimination half-life in a two-compartment model
t_{max}	time to peak concentration
VAS	visual analogue scale
V_{ss}	volume of distribution at steady state
V_z	volume of distribution during elimination
V_1	volume of the central compartment
V_2	volume of the rapid compartment
V_3	volume of the slow compartment

LIST OF ORIGINAL PUBLICATIONS

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

I Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M, Olkkola KT. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol 2011;67:825-831.

ClinicalTrials.gov identifier NCT00837187

II Iirola T, Vilo S, Aantaa R, Wendelin-Saarenhovi M, Neuvonen PJ, Scheinin M, Olkkola KT. Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers. Br J Anaesth 2011;106:522-527.

ClinicalTrials.gov identifier NCT01084473

III Iirola T, Aantaa R, Laitio R, Kentala E, Lahtinen M, Wighton A, Garratt C, Ahtola-Sätilä T, Olkkola KT. Pharmacokinetics of prolonged infusion of high-dose dexmedetomidine in critically ill patients. Crit Care; doi:10.1186/cc10518. Published online ahead of print 26 October 2011.

ClinicalTrials.gov identifier NCT00747721

IV Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen J-P, Scheinin M, Schwilden H, Schüttler J, Olkkola KT. Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth; doi: 10.1093/bja/aer441. Published online ahead of print 25 January 2012.

ClinicalTrials.gov identifier NCT00714857

V Iirola T, Laitio R, Kentala E, Aantaa R, Kurvinen J-P, Scheinin M, Olkkola KT. Highly variable pharmacokinetics of dexmedetomidine during intensive care: a case report. Journal of Medical Case Reports 2010;4:73 (25 February 2010).

ClinicalTrials.gov identifier NCT00714857

1 INTRODUCTION

Most critically ill patients treated in the intensive care unit (ICU) receive analgesic and sedative agents to optimize patient comfort and safety. Benzodiazepines, propofol and opioids are the sedatives that have in recent years most often been used for this purpose (Wunsch *et al.* 2009, O'Connor *et al.* 2010). Still, the use of analgesics, sedatives and antipsychotics in the ICU is associated with adverse events that may prolong the length of stay and may be associated with patient morbidity and poor outcome (Devlin *et al.* 2010). Thus, there is no single ideal sedative or analgesic drug for these patients.

Dexmedetomidine is a selective α_2–adrenoceptor agonist that has until recently been registered in approximately 40 countries for continuous intravenous infusion for sedation of initially intubated and mechanically ventilated adult intensive care patients. The duration and maximum dose of dexmedetomidine infusion in the ICU has been restricted to 24 hours and 0.7 μg/kg/h, respectively (Hospira Inc 2008). However, in September 2011, the European Commission granted marketing authorisation for dexmedetomidine for sedation of adult ICU patients requiring a sedation level not deeper than "arousal in response to verbal stimulation" (Orion Corporation 2011b). In the 27 countries of the European Union, the officially accepted dose of dexmedetomidine was increased to 1.4 μg/kg/h and the restriction of the length of dexmedetomidine administration was replaced with a warning telling that there is no experience of the use of dexmedetomidine for more than 14 days (Orion Corporation 2011a). Additionally, dexmedetomidine has been used for procedural sedation in some countries.

However, off-label use of dexmedetomidine is common. Its official use is limited to adults but it has been used in children as well (Su and Hammer 2011). In addition, the doses used and the durations of the infusions administered have exceeded the recommended ones markedly (Guinter and Kristeller 2010). Moreover, dexmedetomidine has been used, for example, in patients with non-invasive ventilation support (Akada *et al.* 2008), for sedation of spontaneously breathing children during radiological imaging procedures (Mason *et al.* 2008), and as intranasally administered premedication prior to anaesthesia (Yuen *et al.* 2008).

As the bioavailability of dexmedetomidine after intranasal administration and the gastrointestinal effects of dexmedetomidine in humans were not known, it was regarded as important to evaluate these characteristics of dexmedetomidine. Because the pharmacokinetics of dexmedetomidine had previously mainly been investigated in healthy volunteers and in patients receiving rather short and low-dose infusions, it was considered relevant to study its properties in critically ill patients during and after long-lasting, high-dose infusions.

2 REVIEW OF THE LITERATURE

2.1 α_2-Adrenoceptors

Adrenergic receptors (adrenoceptors) mediate the central and peripheral effects of the primary sympathetic neurotransmitter, noradrenaline, and the primary adrenal medullary hormone, adrenaline, as well as several classes of drugs – mainly adrenergic agonists and antagonists. They are members of a large family of cell surface receptors that mediate their actions through interactions with regulatory guanine nucleotide binding proteins (G-proteins). This superfamily of receptors has about 800 members in humans. The rhodopsin-like receptor family is an important subgroup of the G-protein coupled receptors. It contains many important receptors for neurotransmitters and clinically used drugs, such as the muscarinic cholinergic receptors, most of the serotonin receptor subtypes, the dopamine receptors and the adrenoceptors (Fredriksson *et al.* 2003). The G-protein coupled receptors are transmembrane proteins – signalling molecules (ligands) bind to a domain located close to the outer surface of the cell and an intracellular domain activates a G-protein that in turn regulates a cascade of further signalling events and finally causes a functional effect in the target cell (Bockaert and Pin 1999).

Adrenoceptors are found in nearly all peripheral tissues and on many neuronal populations within the central nervous system (Bylund *et al.* 1994). They were originally divided into two major types, α and β, based on their different agonist preferences (Ahlquist 1948). Based on both pharmacological and molecular biology evidence, they are now divided into three major types – α_1, α_2, and β – each of which is further subdivided into three subtypes in humans and other mammalians. (Bylund 2005, Hieble 2007).

The three subtypes of α_2-adrenoceptors - α_{2A}, α_{2B}, and α_{2C} - have distinct patterns of tissue distribution both in the central nervous system and in peripheral tissues. α_{2A}-adrenoceptors are expressed widely in the central nervous system, especially in the locus coeruleus and in other noradrenergic cell body regions (Scheinin *et al.* 1994). They are also expressed in most peripheral tissues, such as the spleen (Perälä *et al.* 1992), pancreas (Peterhoff *et al.* 2003), kidney (Perälä *et al.* 1992), blood vessels (Chotani *et al.* 2004), urethra (Trendelenburg *et al.* 1997), thrombocytes (Galitzky *et al.* 1990b) and fat cells (Galitzky *et al.* 1990a). α_{2B}-adrenoceptors are located mainly in peripheral tissues, being perhaps most abundant in the kidney (Berkowitz *et al.* 1994), placenta (Muthig *et al.* 2007), liver (Berkowitz *et al.* 1994) and smooth muscle of blood vessels (Phillips *et al.* 1997). In the central nervous system, they are found only in the thalamus (Scheinin *et al.* 1994). α_{2C}-adrenoceptors are expressed mainly in the central nervous system, but their expression pattern is different from that of α_{2A}-adrenoceptors (Nicholas *et al.* 1993,

Scheinin *et al.* 1994). However, they can be found also in the kidney (Perälä *et al.* 1992), pancreas (Peterhoff *et al.* 2003), blood vessels (Chotani *et al.* 2004) and adrenal glands (Perälä *et al.* 1992). Examples of the physiological functions and pharmacological responses mediated by α_2-adrenoceptors are presented in Table 1.

Table 1. Examples of the physiological functions and pharmacological responses mediated by α_2-adrenoceptor subtypes, as proposed from experiments with genetically engineered mice.

Receptor	Physiological functions and responses
α_{2A}	Presynaptic inhibition of neurotransmitter release
	Regulation of blood glucose and insulin homeostasis
	Sedation and anaesthesia
	Analgesia
	Inhibition of epileptic seizures
	Bradycardia and hypotension
	Anxiety-like behaviour
	Hypothermia
	Decrease of intraocular pressure
	Inhibition of gastrointestinal motility
α_{2B}	Placental angiogenesis
	Salt-induced hypertension
	Vascular smooth muscle contraction
α_{2C}	Presynaptic inhibition of catecholamine release
	Regulation of dopamine and serotonin balance in the brain
	Modulation of motor behaviour
	Vascular smooth muscle contraction

Modified from Laurila (Laurila 2011).

2.2 Dexmedetomidine

Dexmedetomidine is the dextro-rotatory S-enantiomer of medetomidine, and the drug is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Farmos-Medipolar (later merged to Orion Corporation) and the University of Oulu developed medetomidine in the search for an antihypertensive agent and consequently as a veterinary sedative drug. The active enantiomer dexmedetomidine was selected for clinical development in 1986. The molecular weight of dexmedetomidine hydrochloride is 236.7 g/mol, the empirical formula is $C_{13}H_{16}N_2 \bullet HCl$, and its structural formula is presented in Figure 1. Dexmedetomidine hydrochloride is a white powder that is freely soluble in water and has pK_a of 7.1 (Hospira Inc 2008, Raija Vaheri, Orion Pharma, e-mailed personal communication November 17th 2011).

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with an α_1:α_2 selectivity ratio of 1:1600 (Virtanen *et al.* 1988), and it shows no significant subtype selectivity (Jasper *et al.* 1998, Peltonen *et al.* 1998, Jansson *et al.* 1999). Thus, the effects of dexmedetomidine at clinically relevant concentrations are selectively mediated through α_2-adrenoceptors.

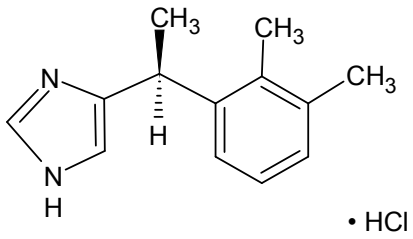


Figure 1. *The structural formula of dexmedetomidine hydrochloride.*

2.3 Pharmacokinetics of dexmedetomidine

2.3.1 Absorption

The bioavailability of dexmedetomidine has been studied after various routes of administration, even though only intravenous administration is officially accepted. After intramuscular, transdermal, buccal and peroral administration, the time to maximum concentration in blood is 12 – 100 min, 6 h, 1.5 h and 2.2 h, and the absolute bioavailability is 73 – 104 %, 88 %, 82 % and 16 %, respectively (Scheinin *et al.* 1992b, Dyck *et al.* 1993b, Kivistö *et al.* 1994, Anttila *et al.* 2003).

2.3.2 Distribution

Both two- and three compartment disposition models have been used to describe the pharmacokinetics of dexmedetomidine (Dyck *et al.* 1993a, Talke *et al.* 1997, Venn *et al.* 2002, Lin *et al.* 2011). Dexmedetomidine exhibits a rapid distribution phase with a half-life of 6-9 min. During the elimination phase, the half-life is approximately 2-3 hours. The volume of distribution at steady state and clearance are approximately 100-170 l and 40-50 l/h, respectively (Karol and Maze 2000, De Wolf *et al.* 2001, Venn *et al.* 2002, Anttila *et al.* 2003). Estimates of multicompartmental pharmacokinetic parameters obtained in previous studies are presented in Table 2.

Table 2. Parameter sets of previous population pharmacokinetic models.

Parameter	Dyck	Lin	Talke	Venn
V_1 (l)	7.99	63.4	16.6	44.1
V_2 (l)	13.8	41.3	85.5	104.5
V_3 (l)	187	284	-	-
Cl_1 (l/min)	0.00791 x HT-0.927	0.47 x (HT/160 cm)$^{6.42}$	0.751	0.82
Cl_2 (l/min)	2.26	2.43	1.37	2.26
Cl_3 (l/min)	1.99	0.086	-	-
V_{ss} (l)	209	389	102	149

V_1, volume of the central compartment; V_2, volume of the rapid compartment; V_3, volume of the slow compartment; Cl_1, systemic clearance; HT, height; Cl_2, rapid distributional clearance; Cl_3, slow distributional clearance; V_{ss}, distribution volume at steady state;. (Dyck et al. *1993a, Talke* et al. *1997, Venn* et al. *2002, Lin* et al. *2011).*

2.3.3 Protein binding

The average protein binding of dexmedetomidine is 94 %, and there is no difference between males and females. Renal dysfunction does not have an effect on protein binding, but hepatic impairment slightly decreases the fraction of dexmedetomidine that is bound to plasma proteins. Therapeutic concentrations of fentanyl, ketorolac, theophylline, digoxin and lidocaine have no significant effects on the plasma protein binding of dexmedetomidine. In vitro studies have suggested that dexmedetomidine does not displace phenytoin, warfarin, ibuprofen, propranolol, theophylline or digoxin from plasma proteins (Karol and Maze 2000).

2.3.4 Metabolism

Dexmedetomidine is metabolized in the liver, and there are three types of initial metabolic reactions, namely conjugation (glucuronidation; Karol and Maze 2000, Ji *et al.* 2004), methylation (Salonen 1991, Hui *et al.* 1997), and oxidation (Orion Corporation 2011a).

Direct N-glucuronidation accounts for approximately one third of dexmedetomidine metabolism, and these glucuronides are the main urinary and circulatory metabolites of dexmedetomidine. N-methyl-dexmedetomidine is produced by methylation, and it is further metabolized to N-methyl dexmedetomidine O-glucuronide (Karol and Maze 2000) that is one of the major circulating products of dexmedetomidine biotransformation (Orion Corporation 2011a). Two minor metabolites, 3-hydroxy-dexmedetomidine and 4-[(S)-1-(2,3-dimethylphenyl)ethyl]-1,3-dihydroimidazol-2-one (H-3), are formed by oxidation (Salonen 1991, Hui *et al.* 1997, Orion Corporation 2011a). 3-hydroxy-dexmedetomidine is further O-glucuronidated (Hui *et al.* 1997, Karol and Maze 2000). Apart from the glucuronides, H-3 is the only metabolite present

in any appreciable quantity in human plasma (Karol and Maze 2000). The formation of the oxidised metabolites is mediated by multiple cytochrome P450 isoforms, especially CYP2A6, but also CYP1A2, CYP2C19, CYP2D6 and CYP2E1 (Karol and Maze 2000, Orion Corporation 2011a). These metabolites of dexmedetomidine have minimal pharmacological activity (Orion Corporation 2011a). Chiral inversion of dexmedetomidine to the inactive levo-enantiomer is of minimal significance in humans (Karol and Maze 2000). The first steps in the proposed metabolic scheme for dexmedetomidine are presented in Figure 2.

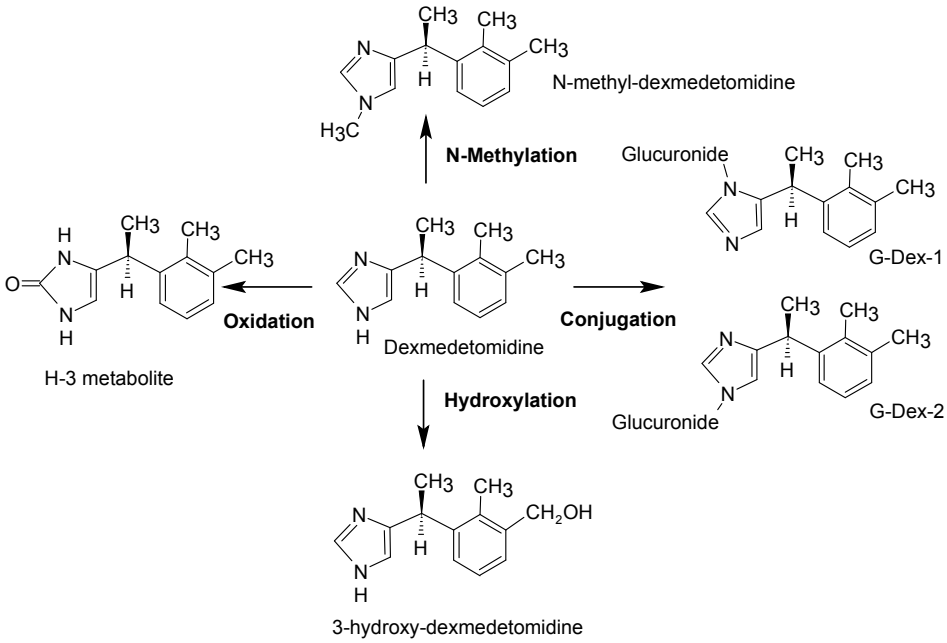


Figure 2. *The first steps in the proposed metabolic scheme for dexmedetomidine (Salonen and Eloranta 1990, Hui et al. 1997, Karol and Maze 2000, Orion Corporation 2011a).*

2.3.5 Elimination

After intravenous infusion of a small dose of radioactive dexmedetomidine, 95% of the radioactivity was excreted in the urine and 4% in the faeces. The N-glucuronides of dexmedetomine and the glucuronide of the 3-hydroxyl-N-methyl metabolite are the main urinary excretion products of dexmedetomidine (Karol and Maze 2000). Less than 1% of the administered dexmedetomidine dose is excreted unchanged in the urine, and 28% of the urinary metabolites are unidentified minor metabolites of dexmedetomidine (Orion Corporation 2011a).

2.3.6 Special populations

In adults, there are no major differences based on gender or age in the pharmacokinetics of dexmedetomidine (Karol and Maze 2000). Pharmacokinetics of dexmedetomidine are not markedly different in subjects with severe renal impairment as defined by a creatinine clearance less than 30 ml/min compared to healthy subjects. However, the sedative effect of dexmedetomidine may be prolonged in subjects with renal dysfunction, probably due to decreased plasma protein binding (De Wolf *et al.* 2001).

Dexmedetomidine clearance values for subjects with mild, moderate and severe liver dysfunction are 74%, 64% and 53% of those in healthy subjects, respectively, and the elimination half-life of dexmedetomidine is 3.9, 5.4 and 7.4 hours in subjects with mild, moderate and severe hepatic impairment, respectively. Additionally, dexmedetomidine plasma protein binding is significantly decreased in subjects with liver dysfunction. (Karol and Maze 2000). Even though dexmedetomidine is dosed to effect, the manufacturer recommends considering dose reduction in patients with liver dysfunction (Orion Corporation 2011a).

In general, dexmedetomidine pharmacokinetics in children is quite similar to that in adults (Petroz *et al.* 2006, Diaz *et al.* 2007, Potts *et al.* 2008, Vilo *et al.* 2008). However, dexmedetomidine clearance changes with age when expressed as l/kg/h being smaller in children younger than 12 months and greater in children aged 1 – 4 years (Potts *et al.* 2009).

2.4 Pharmacokinetic interactions of dexmedetomidine

Theoretically, dexmedetomidine would be expected to decrease the clearance of any drug with a high hepatic extraction ratio, as dexmedetomidine decreases cardiac output (Dutta *et al.* 2000) and therefore also liver blood flow. As dexmedetomidine is metabolized by several cytochrome P450 enzymes, especially CYP2A6, but also by CYP1A2, CYP2C19, CYP2D6 and CYP2E1 (Karol and Maze 2000, Orion Corporation 2011a), drugs inducing or inhibiting these enzymes may influence the pharmacokinetics of dexmedetomidine.

2.5 Pharmacological effects of dexmedetomidine

2.5.1 Sedative effect

The locus coeruleus is an important modulator of vigilance (Aston-Jones *et al.* 1994), and it shows one of the highest densities of α_{2A}-adrenoceptors in the brain (Scheinin *et al.* 1994). Furthermore, it has been shown that the α_{2A}-subtype is the primary mediator of the sedative properties of α_2-agonists (Lakhlani *et al.* 1997). It was shown in an elegant study by Nelson (Nelson *et al.* 2003) that endogenous sleep

pathways are causally involved in dexmedetomidine-induced sedation, as dexmedetomidine-induced sedation resulted in a gene expression pattern in the brain similar to that seen previously during endogenous normal non-rapid eye movement sleep. The observed effects were considered likely to be initiated at the α_2-adrenoceptors as they could be prevented by the selective α_2-antagonist atipamezole and were not observed in genetically modified mice with no α_{2A}-adrenoceptors. Interestingly, systemic but not local administration into the locus coeruleus of the γ-aminobutyric acid receptor type A ($GABA_A$) antagonist gabazine decreased the sedative potency of dexmedetomidine, suggesting that $GABA_A$ receptors may be involved downstream of the locus coeruleus in producing the sedative effect of dexmedetomidine (Nelson *et al.* 2003). It was recently observed in a study that employed positron emission tomography that the sedative effects of dexmedetomidine seemed to be initiated in deep brain structures and only spread to the cerebral cortex at higher drug concentrations (Långsjö *et al.* 2010).

Dexmedetomidine induces dose-related sedative effects in humans. As the dexmedetomidine dose is increased, recall and recognition begin to deteriorate (Ebert *et al.* 2000). Subjects sedated with clinically relevant dexmedetomidine doses remain arousable and are able to communicate if disturbed (Venn *et al.* 1999), although increasing dexmedetomidine doses finally result in unarousability (Ebert *et al.* 2000, Hsu *et al.* 2004). In clinical settings, with recommended dosing dexmedetomidine does not necessarily provide patients with total hypnosis, and therefore, it is not recommended to use dexmedetomidine alone in patients who are also receiving neuromuscular blocking agents (Venn and Grounds 2001).

Dexmedetomidine appears to be as efficacious as lorazepam (Pandharipande *et al.* 2007), midazolam (Riker *et al.* 2009, European Medicines Agency 2011) and propofol (European Medicines Agency 2011). However, there are results suggesting that dexmedetomidine dosed up to 1.4 μg/kg/h is not suitable for deep sedation as a sole sedative (Ruokonen *et al.* 2009) and that increasing the dexmedetomidine dose up to 1.4 μg/kg/h does not necessarily enhance the efficacy of sedation when compared to doses up to 0.7 μg/kg/h (Jones *et al.* 2011).

2.5.2 Analgesic effect

The analgesic effect of α_2-adrenoceptor agonists is mainly mediated via the α_{2A}-adrenoceptor subtype (Hunter *et al.* 1997, Lakhlani *et al.* 1997, Stone *et al.* 1997). In healthy subjects, increasing dexmedetomidine doses lead to linearly decreasing pain sensation and haemodynamic responses to experimental pain (Ebert *et al.* 2000), but the analgesic effect of dexmedetomidine is not as powerful as that of remifentanil (Cortinez *et al.* 2004). However, dexmedetomidine significantly reduces requirements for opioids after major surgery (Arain *et al.* 2004, Barletta *et al.* 2009) and during intensive care (Venn and Grounds 2001). Additionally, intravenous dexmedetomidine prolongs the duration of spinal, epidural and brachial plexus anaesthesia (Coskuner *et al.* 2007, Rutkowska *et al.* 2009, Kaya *et al.* 2010). Interestingly, there is preliminary

evidence suggesting that genetic variation of the α_{2C}-adrenoceptor may affect the analgesic qualities of dexmedetomidine in humans (Kohli *et al.* 2010).

2.5.3 Cardiovascular effects

All subtypes of α_2-adrenoceptors are present in blood vessels (Phillips *et al.* 1997, Chotani *et al.* 2004), and they play important roles in the regulation of the cardiovascular system, as they regulate vasoconstriction and inhibit noradrenaline release from sympathetic nerve endings (Drew and Whiting 1979, Langer 1980). Additionally, α_2-adrenoceptor activation results in reduced sympathetic tone and augmentation of cardiac-vagal activity, with consequent cardiovascular effects (Muzi *et al.* 1992, Toader *et al.* 2009). There are as yet unconfirmed reports that certain genetic variants of α_{2A}- but not α_{2C}-adrenoceptors are associated with the hypotensive response to dexmedetomidine (Kurnik *et al.* 2008, Kurnik *et al.* 2011).

In healthy volunteers, increasing plasma concentrations of dexmedetomidine result in decreased heart rate and cardiac output. As dexmedetomidine concentrations further increase, increases in central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance are observed. The response in the mean arterial pressure is biphasic: first, there is a decrease that is followed by an increase with increasing dexmedetomidine concentrations (Ebert *et al.* 2000, Snapir *et al.* 2006).

After a large enough bolus dose (approximately 1 μg/kg), the haemodynamic response is different. An initial increase of blood pressure is followed by a decrease that reaches its maximum approximately one hour after drug administration. Furthermore, a significant but transient decrease in heart rate can be observed immediately after dexmedetomidine administration, followed by a less pronounced decrease in heart rate for several hours (Kallio *et al.* 1989, Bloor *et al.* 1992). It can be reasoned that the initial increase in blood pressure after a large enough bolus dose is caused by an immediate peripherally induced vasoconstriction due to high plasma dexmedetomidine concentrations (Kallio *et al.* 1989, Bloor *et al.* 1992, Ebert *et al.* 2000) that is soon overridden by the centrally mediated sympatholytic effect resulting in decreased blood pressure. The profound decrease in heart rate during the initial hypertensive phase can be explained by the baroreflex, and the following milder reduction in heart rate is thought to be due to increased parasympathetic tone and reduction in sympathetic tone (Kallio *et al.* 1989, Bloor *et al.* 1992).

In intensive care patients, decreased heart rate is common after dexmedetomidine administration, but the incidence of hypotension in patients receiving dexmedetomidine is similar to that in patients receiving midazolam, lorazepam or propofol (Venn and Grounds 2001, Pandharipande *et al.* 2007, Riker *et al.* 2009, Ruokonen *et al.* 2009). However, hypotension has been associated particularly with a loading dose of dexmedetomidine (Guinter and Kristeller 2010), although also hypertension has been observed after a loading dose (Venn *et al.* 1999).

In healthy subjects, dexmedetomidine reduces myocardial perfusion in parallel with reduced myocardial oxygen demand estimated by rate-pressure product. Dexmedetomidine did not appear to reduce myocardial perfusion in a dose-dependent manner, as the effects were similar at low (0.5 ng/ml) and high (5 ng/ml) plasma dexmedetomidine concentrations. Importantly, the attenuated myocardial perfusion did not result in myocardial ischaemia in healthy volunteers as assessed by ECG and echocardiography (Snapir *et al.* 2006).

2.5.4 Cerebral vascular effects

Dexmedetomidine reduces cerebral blood flow both in animals and in humans (Karlsson *et al.* 1990, Zornow *et al.* 1990, Prielipp *et al.* 2002). However, in some animal studies, the cerebral metabolic rate has been unchanged (Karlsson *et al.* 1990, Zornow *et al.* 1990). This would be deleterious in patients with on-going neurologic injuries, even though dexmedetomidine has also been shown to have neuroprotective qualities (Ma *et al.* 2004). A recent study in healthy volunteers, however, reported that both cerebral blood flow and cerebral metabolic rate were decreased by dexmedetomidine in a dose-related manner, preserving the coupling of cerebral blood flow and cerebral metabolic rate (Drummond *et al.* 2008). It is not known whether this result is valid also in patients with neurological injuries, even though a small study employing brain tissue oxygen partial pressure measurement in surgical patients with neurovascular injuries suggests it (Drummond and Sturaitis 2010). However, the manufacturer of dexmedetomidine strongly recommends considering the potentially deleterious effect of dexmedetomidine when treating patients with severe neurological disorders (Orion Corporation 2011a).

2.5.5 Respiratory effects

In healthy volunteers, even very high dexmedetomidine doses (measured mean plasma dexmedetomidine concentration of 14.7 ng/ml) do not impair arterial oxygenation. Still, small decreases in blood pH and gradual increases in arterial carbon dioxide levels and respiratory rate follow administration of dexmedetomidine in increasing doses (Ebert *et al.* 2000). The lack of clinically significant adverse effects on respiration has been confirmed in further studies in healthy volunteers (Hsu *et al.* 2004) and patients (Venn *et al.* 2000, Venn *et al.* 2002, Martin *et al.* 2003, Cooper *et al.* 2011).

It has been expected that the lack of respiratory depressant effects of dexmedetomidine would shorten the time needed for mechanical ventilation. The time to extubation has been shorter in intensive care patients treated with dexmedetomidine than in those treated with midazolam (Riker *et al.* 2009, European Medicines Agency 2011), but no difference has been observed in the number of ventilator-free days when compared with lorazepam (Pandharipande *et al.* 2007) and in the time needed for mechanical ventilation when compared with propofol (European Medicines Agency 2011).

2.5.6 Sympatholytic and cardioprotective effects

Surgery and intensive care procedures cause stress responses that may be harmful to the patient (Desborough 2000). Dexmedetomidine has potent sympatholytic effects as judged with reduced plasma adrenaline and noradrenaline concentrations in healthy volunteers (Kallio *et al.* 1989, Bloor *et al.* 1992, Ebert *et al.* 2000) and surgical patients (Scheinin *et al.* 1992a, Jalonen *et al.* 1997).

α_2-adrenoceptor agonists (dexmedetomidine, clonidine and mivazerol) were reported to reduce mortality and myocardial ischaemia after major surgery in a Cochrane review (Wijeysundera *et al.* 2009). The effects of α_2-agonists varied with the type of surgery, and the most encouraging results were achieved in vascular surgery, where α_2-agonists reduced mortality, cardiac mortality, and myocardial infarctions. Since the three included drugs have somewhat different selectivity for α_2-adrenoceptors, it is possible that their risk-benefit profiles are not identical. Dexmedetomidine had been used in 11 of the 31 included studies, but no clear differences between the studied drugs could be detected (Wijeysundera *et al.* 2009).

A recent meta-analysis of randomized controlled trials documented that dexmedetomidine is associated with a statistically insignificant trend towards improved cardiac outcome in non-cardiac surgery. However, the authors emphasized that the limitations of the meta-analysis may have prevented the detection of a possible cardioprotective effect (Biccard *et al.* 2008).

2.5.7 Gastrointestinal effects

Generally, α_2-agonists have inhibitory effects on gastric emptying and motility (Fülöp *et al.* 2005). When α_2-agonists are used as premedication, decreased salivary flow is one of the advantages, although it can be classified as an adverse effect in other circumstances (Karhuvaara *et al.* 1991). Previous reports have suggested that dexmedetomidine inhibits gastric emptying and gastrointestinal transit in rats (Asai *et al.* 1997a, Asai *et al.* 1998). In a previous study, dexmedetomidine did not significantly inhibit gastric emptying compared with propofol in intensive care patients (Memis *et al.* 2006).

2.5.8 Miscellaneous effects

As an imidazole compound, dexmedetomidine has the potential to have inhibitory effects on cortisol synthesis similar to etomidate. It has been shown in dogs that the cortisol response to adrenocorticotrophic hormone is blunted three hours after a dexmedetomidine bolus of 80 μg/kg (Maze *et al.* 1991). However, hypocortisolism has not been an issue after clinically relevant dexmedetomidine doses in healthy volunteers, surgical patients or patients needing post-operative intensive care (Kallio *et al.* 1989, Aho *et al.* 1992, Venn *et al.* 2001).

α_{2A}-adrenoceptors are involved in the regulation of blood glucose homeostasis, and dexmedetomidine lowers insulin and elevates glucose levels in mice (Fagerholm *et al.* 2004). It has been shown that there is a tendency for low insulin concentration in post-operative intensive care patients (Venn *et al.* 2001) and hyperglycemia in intensive care patients after dexmedetomidine administration (Riker *et al.* 2009). However, both hyperglycemia and hypoglycemia are mentioned as common (≥ 1/100 to < 1/10) adverse reactions in the summary of product characteristics of dexmedetomidine (Orion Corporation 2011a).

Clonidine has traditionally been used to treat postoperative shivering (Kranke *et al.* 2002). Dexmedetomidine seems to have the same anti-shivering property, as it has decreased the incidence of shivering after general and spinal anaesthesia (Elvan *et al.* 2008, Usta *et al.* 2011) and been used to treat shivering during therapeutic hypothermia (Choi *et al.* 2011). As suggested by the commonly known effects of α_2-agonists, also dexmedetomidine decreases intraocular pressure during ophthalmic surgery under local anaesthesia (Abdalla *et al.* 2006).

It has been shown in mice that clonidine and dexmedetomidine protect against contrast medium-induced nephropathy by preserving outer medullary renal blood flow as quantified using laser-Doppler flow probes (Billings *et al.* 2008). Additionally, dexmedetomidine inhibits vasopressin secretion, causing water diuresis in anaesthetized dogs, which might be beneficial during ischemic events (Villela *et al.* 2005). The increasing effect of dexmedetomidine on urinary output has been observed in thoracotomy (Frumento *et al.* 2006) and heart surgery patients (Leino *et al.* 2011), but no clear clinical renal benefit has been shown.

2.6 Therapeutic uses of dexmedetomidine

Dexmedetomidine has been indicated for sedation lasting up to 24 hours of initially intubated and mechanically ventilated adult intensive care patients and in some countries for sedation of non-intubated adult patients prior to and/or during surgical and other procedures. The package insert for those marketing authorisations stated that it is recommended to initiate dexmedetomidine infusions at 1 μg/kg over 10 minutes followed by maintenance infusions of 0.2 to 0.7 μg/kg/h for intensive care sedation and at 1 μg/kg over 10 minutes followed by maintenance infusions of 0.2 to 1 μg/kg/h for procedural sedation (Hospira Inc 2008).

The use of dexmedetomidine in non-intubated patients requiring sedation for surgical or other procedures has included, for example, laryngeal surgery (Jense *et al.* 2008), awake fiberoptic intubation (Tsai *et al.* 2010), dental procedures (Ustun *et al.* 2006), ophthalmologic procedures (Ayoglu *et al.* 2007), and carotid endarterectomy (McCutcheon *et al.* 2006).

In addition to its use for officially approved indications, off-label use of dexmedetomidine has been common. Both the doses and the durations of dexmedetomidine infusions have exceeded the official ones markedly (Guinter and Kristeller 2010). Indeed, the European Commission has granted in September 2011 centralised marketing authorisation for dexmedetomidine indicated for sedation of adult ICU patients (Orion Corporation 2011b) allowing dexmedetomidine dose rates of 0.2 – 1.4 μg/kg/h. However, no loading dose is recommended in the European marketing authorisation, because no loading dose was given in the active comparator studies referred to in the registration process (European Medicines Agency 2011). The duration of administration has not been restricted in these 27 European Union countries, but it is emphasized that there is no experience of the use of dexmedetomidine for more than 14 days and that eventual use for longer periods than that should be regularly reassessed (Orion Corporation 2011a).

Dexmedetomidine has been used in paediatric intensive care patients as well. The dosing has exceeded the official limits in the same manner as in adults: dexmedetomidine has been infused to children for several days (Carroll *et al.* 2008, Bejian *et al.* 2009) with doses more than three-fold compared to the recommended ones (Carroll *et al.* 2008), and the youngest patients being only 1 day old (Bejian *et al.* 2009). However, based on the available very limited published information, dexmedetomidine has seemed to be safe in children (Carroll *et al.* 2008, Vilo *et al.* 2008, Bejian *et al.* 2009).

Since α_2-agonists have many theoretically favourable effects, feasibility of dexmedetomidine as an anaesthetic adjunct has also been studied. Promising results have been seen in neurosurgical operations requiring intraoperative active patient participation (awake craniotomy) (Mack *et al.* 2004), cardiac surgery (Jalonen *et al.* 1997), and bariatric surgery (Tufanogullari *et al.* 2008).

Dexmedetomidine has been used in various groups of spontaneously breathing patients in the ICU. Dexmedetomidine infusions have been shown to provide effective sedation during noninvasive ventilation support and to lead to an increased rate of success (Akada *et al.* 2008). It seems to cause less delirium than benzodiazepines (Pandharipande *et al.* 2007, Riker *et al.* 2009), and it has successfully been used in treating delirium and agitation in non-intubated intensive care patients at our institution (Juha Perttilä, personal communication November 29th 2011). Additionally, it has been used in treating iatrogenic opioid abstinence symptoms in critically ill patients (Honey *et al.* 2009) and alcohol withdrawal symptoms (Stern *et al.* 2010). Dexmedetomidine has been proposed to be used in the treatment of delirium at the end of life and terminal sedation (Prommer 2010), in addition to the management of refractory pain in palliative care settings (Coyne *et al.* 2010).

The favourable safety profile of dexmedetomidine, especially the lack of respiratory depression, has enabled its use in radiological imaging procedures in children. To reach the desired level of sedation, dexmedetomidine has been infused to children in high

doses. There are dosing schemes that allow radiology nurses to give repeated bolus doses of 3 μg/kg over three 10 min periods to achieve Ramsey Sedation Scores of 4 and then start a continuous infusion of 2 μg/kg/h (Mason *et al.* 2010). Even though these high doses are associated with moderate decreases in heart rate and moderate changes in blood pressure, they have not been associated with adverse sequelae (Mason *et al.* 2008).

Intranasal dexmedetomidine has been shown to be a useful alternative for oral midazolam as premedication in children (Yuen *et al.* 2008, Talon *et al.* 2009) and a promising sedative in dental surgery (Cheung *et al.* 2011). The onset of sedation after intranasal administration has been reported to occur at 45 min in healthy volunteers (Yuen *et al.* 2007) and at 25 min in children (Yuen *et al.* 2010). Additionally, oral and buccal dexmedetomidine have been used successfully for premedication of surgical patients (Zub *et al.* 2005, Sakurai *et al.* 2010).

Positive experiences in the treatment of pain with clonidine have inspired physicians to assess the analgesic effects of dexmedetomidine. Systemically administered dexmedetomidine does not provide sufficient pain control as a sole analgesic agent, but through synergistic mechanisms, it plays a part in multimodal analgesia and with it opioid consumption and their adverse effects may be reduced (Lin *et al.* 2009). There are conflicting results on the neurotoxicity of dexmedetomidine (Brummett *et al.* 2008, Konakci *et al.* 2008, Brummett *et al.* 2009), but there are promising reports on the use of dexmedetomidine as an adjunct in intrathecal (Kanazi *et al.* 2006), epidural (Elhakim *et al.* 2010), caudal (El-Hennawy *et al.* 2009), and perineural (Esmaoglu *et al.* 2010) anaesthesia. Additionally, dexmedetomidine has been administered intra-articularly (Al-Metwalli *et al.* 2008) and as an adjunct of intravenous regional anaesthesia (Memis *et al.* 2004).

2.7 Adverse effects of dexmedetomidine

The adverse effects of dexmedetomidine are predictable from the commonly known effects of α_2-adrenoceptor agonists. According to the most recent information provided by the manufacturer of dexmedetomidine, the most frequently reported adverse events are hypotension, hypertension and bradycardia, occurring in 25%, 15% and 13% of patients, respectively (Orion Corporation 2011a). Bradycardia has been commonly associated with dexmedetomidine in double-blind randomized studies in intensive care patients, but patients on dexmedetomidine sedation have not had more often hypotension than those sedated with midazolam or lorazepam (Pandharipande *et al.* 2007, Riker *et al.* 2009). In a recent study (Ruokonen *et al.* 2009), there was no difference in the incidence of hypotension between patients receiving dexmedetomidine and those receiving standard care (propofol or midazolam). The effect of dexmedetomidine dose on the incidence of hypotension is not clear, as there

are conflicting reports (Devabhakthuni *et al.* 2011, Jones *et al.* 2011). Hypertension has often been associated with loading doses of dexmedetomidine (Venn *et al.* 1999).

In the pooled data of clinical trials in intensive care, consisting of 3137 randomized patients, bradycardia, hypotension and hypertension are ranked as very common (≥ 1/10) and hyperglycaemia, hypoglycaemia, agitation, myocardial ischaemia or infarction, tachycardia, nausea, vomiting, dry mouth, withdrawal syndrome and hyperthermia are ranked as common (≥ 1/100 to <1/10) adverse effects (Orion Corporation 2011a).

2.8 Population pharmacokinetic analysis

In traditional pharmacokinetic studies, the study subjects are usually healthy volunteers or patients selected by using complex inclusion and exclusion criteria. However, patients are not a homogenous group, and results derived from studies performed in highly selected subpopulations are not necessarily valid in real-life patients, as many features like body weight, kidney and liver function, circulatory status, and presence of other therapies and illnesses can affect the dose-concentration relationship. Therefore, it has been considered appropriate to develop means to explain variation on the basis of differing biological characteristics (Wright 1998, U.S. Department of Health and Human Services 1999).

Classically, pharmacokinetic parameters like clearance and half-life are determined after extensive blood sampling from each study subject, and these individual structural parameters are subsequently treated as variables and summarized using statistical estimates, such as the sample mean and standard deviation (Wright 1998). The major problem of this approach is that it does not consider separately the two major sources of population variability – intraindividual variability and interindividual variability. Intraindividual variability is caused by imprecision of the employed methods or actual biological variability in the individual himself. In turn, interindividual variability results partly from predictable differences between individuals, based e.g. on factors such as age and body weight (fixed effects). Even after considering all known covariates, some variability still exists. This remaining unexplained variability between individuals is called random effects. Thus, a sophisticated statistical analysis method called non-linear mixed-effect modelling is used to separate these fixed and random effects and to reveal the sources and explanations of population variability (Heeremans *et al.* 2010).

A remarkable benefit of the population pharmacokinetic approach is that it can be used in studies where only a few blood samples are drawn from each subject at different time points, because the process does not require that each individual in the study provides sufficient data to completely characterize his pharmacokinetic profile, as the analysis methods allow borrowing of information between individuals to fill in the gaps. This makes population pharmacokinetics especially well suited for phases 3 and

4 of clinical drug development and for vulnerable populations like children in whom it is not possible to collect large numbers of samples (U.S. Department of Health and Human Services 1999, Heeremans *et al.* 2010, Duffull *et al.* 2011). Therefore, population pharmacokinetics has become practically synonymous with the design, execution and analysis of pharmacokinetic studies involving sparse data, even if the same analysis techniques can equally well be applied to data obtained from a conventional pharmacokinetic study (Aarons 1991).

The complexity of the employed statistical analysis is a major disadvantage of population pharmacokinetics. Still, population-based modelling is now considered by many as superior to older, more traditional modelling methods (Heeremans *et al.* 2010).

3 AIMS OF THE STUDY

The general objectives of the present studies were to determine the bioavailability of dexmedetomidine after intranasal administration, to critically evaluate the gastrointestinal effects of dexmedetomidine, and to characterize the pharmacokinetics of dexmedetomidine in critically ill intensive care patients.

The specific objectives of the studies were:

1. To compare the pharmacokinetics and pharmacodynamics of dexmedetomidine in healthy volunteers after intranasal and intravenous administration and to determine the optimal timing of intranasal administration (Study I).

2. To characterize the effects of dexmedetomidine on gastrointestinal motility in healthy volunteers (Study II).

3. To characterize the pharmacokinetics of long-lasting dexmedetomidine infusions in intensive care patients and to assess the dose linearity and safety of doses higher than those advised by the manufacturer at the time of the study (0.7 – 2.5 μg/kg/h) (Studies III and V).

4. To explore the effects of patient factors on the pharmacokinetics of dexmedetomidine in doses higher than those advised by the manufacturer at the time of the study (0.7 – 2.5 μg/kg/h) in intensive care patients using population pharmacokinetic methods (Study IV).

4 MATERIALS AND METHODS

4.1 Subjects

Altogether 19 healthy volunteers and 34 intensive care patients participated in Studies I-II and III–IV, respectively. Study V is a case report presenting a single patient included in Study IV. The number of subjects and their demographics are presented in Table 3. The characteristics of the intensive care patients are presented in more detail in Table 4.

Table 3. Characteristics of study subjects in Studies I–IV.

	Type of subjects	Sex M/F	Age (years)	Weight (kg)	BMI (kg/m^2)
I	Healthy volunteers	7 / 0	21 (19-25)	83 (60-86)	25 (20-27)
II	Healthy volunteers	12 / 0	21 (20-26)	77 (61-85)	23 (20-25)
III	ICU patients	8 / 5	57 (18-82)	85 (56-120)	29 (21-38)
IV	ICU patients	16 / 5	60 (22-85)	85 (53-120)	28 (20-37)

M, male; F, female; BMI, body mass index; ICU, intensive care unit; data are given as number or median (range).

4.1.1 Studies I and II

Healthy, non-smoking male volunteers were recruited via internet advertisements directed to university students. After reading the announcement, subjects interested in participating in the study contacted the investigator by e-mail and received more information about the study. If they were still willing to participate in the study, they were invited to a personal visit.

During the preliminary visit, volunteers were first informed about the study protocol in detail. Then, after informed consent, they were ascertained to be in good health through medical history, clinical examination including auscultation of the lungs and the heart, measurement of blood pressure and palpation of the abdomen, and laboratory tests (haemoglobin, haematocrit, red blood cell count, white blood cell count, platelets, creatinine, urea, bilirubin, 12-lead electrocardiogram). Additionally, in Study II, a urine test for drugs with addiction potential was performed and the risk to develop opioid addiction was assessed using the Abuse Questions (Table 5 (Michna *et al.* 2004)). The inclusion and exclusion criteria are presented in Tables 6 and 7.

Table 4. Characteristics of the 34 intensive care patients.

	Patient	Age (years)	Weight (kg)	SAPS II	Bilirubin (μmol/l)	Creatinine (μmol/l)	Day	Vaso-pressors
Study III	1	75	80	48	40	79	1.1	Yes
	2	69	90	68	11	179	1.1	Yes
	3	50	120	38	8	186	1.1	Yes
	4	18	56	34	14	45	2.7	Yes
	5	59	85	39	< 5	163	1.1	Yes
	6	53	90	40	109	112	1.1	No
	7	82	60	47	10	175	3.6	Yes
	8	77	60	47	5	44	2.5	Yes
	9	74	85	73	91	156	1.8	Yes
	10	42	105	42	17	97	1.3	Yes
	11	57	110	55	-	-	1.5	Yes
	12	56	80	29	12	77	4.9	Yes
	13	35	100	22	15	72	0.9	Yes
	Mean	**57.4**	**86.2**	**44.8**	**15.5***	**103***	**1.6***	
	CV (%)	**32.1**	**22.8**	**31.9**	**153**	**56.2**	**58.3**	
Study IV	1	67	75	38	20	68	0.6	Yes
	2	73	78	37	11	39	2.3	No
	3	35	70	46	8	46	2.6	Yes
	4	42	89	57	16	126	14.5	No
	5	60	88	78	122	270	10.4	Yes
	6	37	53	24	11	27	14.7	Yes
	7	49	90	33	11	43	2.9	Yes
	8	81	88	42	13	236	2.9	Yes
	9	54	63	43	11	90	5.4	Yes
	10	72	82	53	30	100	1.3	Yes
	11	85	89	45	5	217	0.8	Yes
	12	63	90	57	46	309	0.9	Yes
	13	58	75	20	< 5	93	0.9	Yes
	14	65	87	29	5	167	1.5	Yes
	15	54	70	39	< 5	52	5.7	Yes
	16	22	95	26	7	63	1.3	Yes
	17	62	85	46	13	54	0.6	Yes
	18	48	120	44	< 5	48	4.5	No
	19	77	80	48	19	175	7.8	Yes
	20	79	87	50	6	70	1.1	Yes
	21	52	70	38	8	45	0.6	Yes
	Mean	**58.8**	**82.1**	**42.5**	**10.5***	**86.7***	**2.3***	
	CV (%)	**28.0**	**16.6**	**30.6**	**122**	**81.6**	**144**	

*Bilirubin and creatinine values refer to the highest value (μmol/l) during dexmedetomidine infusion. The variable day refers to the day dexmedetomidine infusion was commenced after ICU admission. Vasopressors indicate if the patient received vasoactive drugs prior to dexmedetomidine infusion. Bilirubin values < 5 were treated as equal to 2.5. SAPS II, Simplified Acute Physiology Score (Le Gall et al. 1993); CV, coefficient of variation; * geometric mean.*

Table 5. Abuse Questions (Michna et al. 2004).

1.	Is there a history of alcohol or substance abuse in your family, even among your grandparents, aunts, or uncles?
2.	Have you ever had a problem with drugs or alcohol or attended an Alcoholics Anonymous or Narcotics Anonymous meetings?
3.	Have you ever had any legal problems or been charged with driving while intoxicated or driving under the influence?

The participants of Studies I and II were instructed to refrain from the use of any drugs known to cause enzyme induction or inhibition for a period of 30 days, any drugs or natural products (including grapefruit products) for at least 14 days and alcohol and caffeine-containing products for at least 24 hours prior to the study. Paracetamol and ibuprofen could be used to treat an occasional headache or other similar condition in Studies I and II, respectively.

In Study II, the following additional restrictions were employed: the subjects were not allowed to eat foods rich in fibre or long-chain carbohydrates (such as rye bread, porridge, other full grain products, pasta, vegetables, fruits, berries) on the day before each study session, eating and physical exercise were not allowed for 12 hours, water intake for four hours and sleeping for an hour before the session start.

4.1.2 Studies III and IV

Studies III and IV were conducted in the 24-bed mixed intensive care unit of Turku University Hospital from October 2007 until February 2009. All patients admitted to the ICU were considered for enrolment, but no other active recruitment procedures were used. The patients admitted into the ICU were evaluated preliminarily, and if they seemed eligible for the study, informed consent was sought from the study subject candidate's legal representative and then study screening procedures were performed. All study subjects for whom informed consent was received and who fulfilled all inclusion criteria but none of the exclusion criteria (Tables 6 and 7) were entered into the study.

Table 6. The inclusion criteria of Studies I–IV.

Study I	**Study II**
Age ≥ 18 years and weight ≥ 60 kg	Age ≥ 18 years and weight ≥ 60 kg
Male gender	Male gender
Fluency in the Finnish language	Normal cognitive function and fluency in the Finnish language
Written informed consent from the subject	Written informed consent from the subject
Study III	**Study IV**
Age ≥ 18 years	Age ≥ 18 years
Sedated and ventilated in ICU; sedation is expected to be clinically required for at least 24 hours	Need for dexmedetomidine sedation, as determined by the responsible physician
Prescribed light to moderate sedation (RASS = 0 to -3)	Predicted length of dexmedetomidine sedation ≥ 48 hours
Written informed consent from the patient's legal representative	Written informed consent from the patient's legal representative

ICU, intensive care unit; RASS, Richmond Agitation Sedation Scale (Sessler et al. 2002).

Table 7. The exclusion criteria of Studies I–IV.

Common exclusion criteria of Studies I and II
Previous history of intolerance to the study drug or related compounds and additives
Existing or recent significant disease
History of haematological, endocrine, metabolic or gastrointestinal disease
History of asthma or any kind of drug allergy
Special diet or lifestyle factors which would compromise the conditions of the study or the interpretation of the results
Donation of blood within six weeks prior to and during the study
BMI > 30 kg/m^2
Previous or present alcoholism, drug abuse, or psychological or other emotional problems that are likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements
Participation in any other clinical study involving investigational or marketed drug products concomitantly or within one month prior to the entry into this study
Smoking during one month before the start of the study or during the study period
Clinically significant abnormal findings in physical examination, ECG or laboratory screening

Further exclusion criteria in Study I	Further exclusion in Study II
Concomitant drug therapy of any kind except paracetamol in the 14 days prior to the study days	Concomitant drug therapy of any kind except ibuprofen in the 14 days prior to the study days A positive test result in urine for drugs of abuse A "yes" answer to any of the questions in a modified Finnish version of the Abuse Questions

Exclusion criteria in Study III
Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury
Uncompensated acute circulatory failure at screening (severe hypotension with MAP < 55 mmHg despite therapy with vasopressor and inotrope)
Heart rate < 50 beats/min for longer than 5 min between screening and start of study treatment
Atrioventricular conduction block II-III (unless pacemaker installed)
Severe hepatic impairment (e.g. bilirubin > 101 μmol/l)
Need for continuous muscle relaxation
Any condition which would significantly interfere with the collection of study data
Burn injuries or other conditions requiring repetitive anaesthesia or surgery
Use of centrally acting α_2–adrenoceptor agonists or -antagonists within 24 hours prior to starting the study
Known allergy to dexmedetomidine or any excipient of the study treatment
Patients who have or are expected to have treatment withdrawn or withheld due to poor prognosis
Patients receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy)
Patients unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome)
Patients who are unlikely to be weaned from mechanical ventilation
Positive pregnancy test or currently lactating
Received any investigational drug within the preceding 30 days
Concurrent participation in any other interventional study
Previous participation in this study
Any other condition which, in the investigator's opinion, would make it detrimental for the subject to participate in the study

Exclusion criteria in Study IV
Previous history of intolerance to the study drug or related compounds and additives
Existing significant haematological, endocrine, metabolic or gastrointestinal disease

MAP, mean arterial pressure; BMI, body mass index.

4.2 Study designs

4.2.1 Study I

Study I had a two-period, cross-over design with balanced randomization. As a proof-of-concept study, it was decided that at least six subjects had to undergo two evaluable treatment periods for study completion. Initially, eight subjects were recruited to the study. Six of the eight subjects were allocated into the study group and two remained in reserve to replace subjects in case of a common cold or other condition jeopardizing the reliability of the results after intranasal administration of dexmedetomidine or withdrawal of an individual for some reason. Indeed, one subject informed in the morning of the second study day that he had caught a common cold. Therefore, a reserve subject replaced him in that study session. Once the subject with the flu had recovered, a third study session was arranged for him and the replacing subject. Consequently, seven subjects participated in both treatment periods. Intranasal administration of dexmedetomidine failed in one subject because of a handling error of the nasal application device. This study subject was excluded from the analysis. Thus, seven study subjects participated in the study but only six subjects successfully completed the study and were included in the analyses.

A venous catheter was inserted into a large forearm vein for administration of dexmedetomidine and other drugs potentially needed to treat adverse events. An arterial catheter was inserted into the radial artery for blood sampling and blood pressure monitoring. ECG, invasive blood pressure and peripheral arteriolar oxygen saturation (SpO_2) were monitored continuously for safety purposes. The study subjects were given dexmedetomidine once intravenously and once intranasally in a randomized order.

Pharmacokinetic parameters were calculated after the two routes of administration. Heart rate, systolic and diastolic blood pressure, and adrenaline and noradrenaline concentrations in plasma were measured to assess the sympatholytic effects of dexmedetomidine. The Maddox wing test (Hannington-Kiff 1970) was used to measure the effect of dexmedetomidine on the coordination of the extraocular muscles, and the Bispectral Index (BIS) was used to monitor the level of sedation (Sigl and Chamoun 1994). Subjective effects were recorded with horizontal visual analogue scales (VAS) (Bond and Lader 1974). Additionally, the local tolerability of intranasally administered dexmedetomidine was assessed with VAS and by inspection of the nasal mucosa.

4.2.2 Study II

Study II had a three-period cross-over design with balanced randomization. On the basis of previous studies (Memis *et al.* 2006), it was calculated that 10 subjects would be required to demonstrate a 30% difference in paracetamol $AUC_{0–90\ min}$ between the placebo and dexmedetomidine phases at a level of significance of $p = 0.05$ and power of 80%. In the study of Memis et al., the mean value for paracetamol $AUC_{0\ –\ 120\ min}$ in the control group was 895 min mg/l with a standard deviation of 500 min mg/l. For

calculation of the sample size, it was assumed that the standard deviation of the difference between the phases would be equal to the mean value of the difference. Hence, 12 healthy volunteers were enrolled in the study after written informed consent.

The 12 subjects were given dexmedetomidine, morphine and placebo in a randomized order. The wash-out period between consecutive administrations was at least seven days. A venous catheter was inserted into a large forearm vein for study drug administration and another into an antecubital vein in the opposite extremity for blood sampling. ECG, non-invasive blood pressure and arteriolar oxygen saturation (SpO_2) were monitored for safety purposes.

After running the infusions for 30 min, the subjects were given orally 1 g of paracetamol (Panadol Forte® tablet, GlaxoSmithKline Consumer Healthcare A/S, Copenhagen, Denmark) with 100 ml of tap water (25 °C) and 10 g of lactulose in solution (Laktulos Merck NM® 667 mg/ml, Merck NM AB, Stockholm, Sweden) with 50 ml of tap water. Gastric emptying and gastrointestinal transit were assessed after the three different treatments by using the paracetamol absorption test (Heading *et al.* 1973) and the hydrogen breath test (Read *et al.* 1985, Eisenmann *et al.* 2008), respectively.

4.2.3 Studies III and IV

Studies III and IV had an open-label design with no comparator. On empirical grounds, it was planned to recruit 12 - 20 patients so that at least six of the patients would have a minimum duration of five days of dexmedetomidine infusion, and 25 – 30 patients to obtain a sufficient number of blood samples for the analysis in Studies III and IV, respectively.

The patients were cannulated and monitored according to the routine care of the ICU. Blood samples were drawn for pharmacokinetic analysis. In Study III, the depth of sedation was assessed once daily, and adverse events, heart rate, blood pressure, ECG and laboratory parameters were used as safety and tolerability variables. In Study IV, all available information including age, body mass, height, cardiac index, possible ventilator therapy and routine laboratory parameters were considered to be used as covariates. Heart rate and blood pressure were recorded to assess the pharmacodynamic effects of dexmedetomidine.

4.3 Dexmedetomidine, morphine and placebo dosing

Drug dosing in Studies I – IV is summarized in Table 8. In Study I, a more concentrated veterinary formulation of dexmedetomidine (dexmedetomidine hydrochloride 500 μg/ml) was used for intranasal administration in order to keep the volume of the aerosol dose small enough. The intranasal aerosol dose was administered using a nasal spray application system (Spray Pump VP7/100S, 0.1 ml/dose, Valois Pharma, Le Vaudreuil, France) – one 0.1 ml dose into each nostril.

Table 8. Drug dosing in Studies I - IV

Study	Dexmedetomidine	Comparator(s)
I	An intranasal dose of 84 μg of dexmedetomidine using a nasal spray application system	An intravenous dose of 84 μg of dexmedetomidine over 10 min
II	An intravenous loading dose of 1 μg/kg of dexmedetomidine over 20 min followed by an infusion of 0.7 μg/kg/h for 190 min	A. 0.10 mg/kg of morphine infused intravenously over 20 minutes, followed by a placebo (0.9 % saline) infusion for 190 min B. Placebo (0.9 % saline) infused intravenously in the same manner as the active drugs
III	A constant-rate intravenous infusion for 12 hours followed by an infusion of 0.1 – 2.5 μg/kg/h using predefined dose levels to maintain sedation in range 0 to -3 using the RASS for a maximum of 14 days	Not used
IV	An intravenous loading dose of 0.5 - 1 μg/kg over 10 min followed by an infusion of 0.1–2.5 μg/kg/h on the basis of clinical need for as long as the responsible physician deemed necessary	Not used

RASS, Richmond Agitation-Sedation Scale (Sessler et al. 2002). In Study III, the rate of the constant rate infusion was determined by the pre-study dose of propofol or midazolam.

In Study III, the rate of the 12-hour constant rate dexmedetomidine infusion was determined by the pre-study dose of propofol or midazolam as follows: a dose of 0.1, 0.2, 0.45 or 0.7 μg/kg/h of dexmedetomidine was considered to be equivalent to <0.3, 0.3-0.79, 0.8-1.59 and >1.6 mg/kg/h of propofol or <0.03, 0.03-0.06, 0.06-0.09 and >0.09 mg/kg/h of midazolam, respectively. Downward titration was allowed in case of excessive sedation or an adverse event. After the first 12 h, the infusion rate of dexmedetomidine was titrated as needed between a minimum of 0.1 and a maximum of 2.5 μg/kg/h by titrating the dose stepwise upwards or downwards to maintain sedation in the range of 0 to -3 using the Richmond Agitation-Sedation Scale RASS (Sessler *et al.* 2002). Only predefined dose levels of 0.1, 0.2, 0.45, 0.7, 0.95, 1.2, 1.4, 1.7, 2.1 and 2.5 μg/kg/h of dexmedetomidine were used.

4.4 Concomitant treatments

In Studies I and II, there were no concomitant treatments. In Studies III and IV, all concomitant treatments were recorded. In Study III, propofol or midazolam, and in Study IV, propofol, midazolam, lorazepam or haloperidol were given if required as rescue therapy to maintain sedation at the desired level. Otherwise, the patients received standard care of the unit, which included, for example, administration of oxycodone, fentanyl or remifentanil for pain relief.

4.5 Blood sampling

Blood sampling for pharmacokinetic assessment in Studies I–IV is presented in Table 9. Additionally in Study III, blood samples were collected for safety assessment on days 2, 4, 6, 9 and 14. These included complete blood count, glucose, urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, troponin T, total protein, triglycerides, total cholesterol, sodium, potassium, calcium, chloride and cortisol. In Study IV, all results of routine laboratory tests could be used as covariates.

Table 9. Blood sampling for pharmacokinetic assessment in Studies I–IV.

Study	Sampling schedule
I	Immediately prior to dexmedetomidine administration and thereafter at 5, 10, 15, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8 and 10 h.
II	Immediately prior to paracetamol administration and thereafter at 10, 20, 30, 40, 50, 60, 70, 80 min and 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5 and 4 h.
III	Immediately prior to dexmedetomidine administration and thereafter at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8 and 12 h. Subsequently, three times a day in the morning, afternoon and evening, and immediately before stopping dexmedetomidine infusion and thereafter at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, 15, 18, 24, 36 and 48 h. In case of haemodiafiltration, immediately before commencement of the treatment followed by concomitant samples from the afferent and efferent limbs of the filter circuit at 2, 4, 6 and 8 h.
IV	Immediately prior to dexmedetomidine administration and thereafter at 5, 7.5, 10, 15, 20, 30, 45, 60, 90 and 120 min. Subsequently, three times daily at 6 - 10 hour intervals.

4.6 Analysis of drug and catecholamine concentrations in plasma

4.6.1 Dexmedetomidine and its H-3 metabolite

Concentrations of dexmedetomidine and its H-3 metabolite in plasma were measured at the Department of Pharmacology, Drug Development and Therapeutics, University of Turku and Unit of Clinical Pharmacology, TYKSLAB, Turku, Finland. The reference compound in the drug concentration analysis was dexmedetomidine HCl and the internal standard was deuterated medetomidine, $^{2}H_{6}$-medetomidine HCl, both provided by Orion Pharma (Espoo, Finland). Sample preparation was performed using solid phase extraction. Aliquots of 0.10 ml of ethylenediaminetetraacetic acid plasma were mixed with 0.85 ml of 0.1 % formic acid in water and 50 µl of internal standard solution and extracted with Sep-Pak® Vac 1cc (100 mg) tC18 cartridges (Waters Corporation, Milford, MA, USA).

The employed analysis method for dexmedetomidine was based on a previously described procedure (Ji *et al.* 2004, Snapir *et al.* 2006). Isocratic high-performance liquid chromatography separation was performed with a Phenomenex Gemini C_{18} 150 x 2.0 mm (5 µm) column (Torrance, CA, USA) and a mobile phase consisting of methanol and 0.1 % formic acid in water (140:80) at 28 °C. In Studies I and III, the mobile phase also contained acetonitrile, but this was later omitted as unnecessary. Mass spectrometric detection was carried out with an Applied Biosystems API 4000 triple-quadrupole instrument (AB SCIEX, Foster City, CA, USA), using positive ion spray ionisation and multiple reaction monitoring. The precursor ion – fragment ion pairs detected were *m*/*z* 201.1 – 95.0 for dexmedetomidine and *m*/*z* 206.2 – 95.1 for the internal standard. In one of the studies (III), also a minor pharmacologically inactive metabolite of dexmedetomidine, H-3, was quantitated. This was performed in the same analysis runs with the parent compound. Deuterated H-3 was used as an additional internal standard for this purpose (Orion Pharma). Quantitation was based on peak area ratios of the analyte(s) and the internal standard(s). Data collection and analysis were done with Applied Biosystems Analyst 1.4.1 software.

The assay was validated and found to be linear over a concentration range from 0.020 to 10.0 ng/ml. Within-run precision was assessed using six determinations per dexmedetomidine concentration at four concentration levels, 0.020, 0.060, 0.90 and 8.0 ng/ml, and was found to be acceptable (the coefficient of variation was 9.5 % at 0.020 ng/ml and 1-3 % at the other levels). The between-batch precision was also evaluated at the same concentration levels. The coefficient of variation was less than 8 % at all concentration levels.

4.6.2 Paracetamol

The plasma paracetamol concentrations were analyzed at the Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, by using reversed-phase high-performance liquid chromatography (Pufal *et al.* 2000). The lower limit of plasma paracetamol quantitation was 0.1 mg/l.

4.6.3 Adrenaline and noradrenaline

Concentrations of adrenaline and noradrenaline in plasma were measured at the Department of Pharmacology, Drug Development and Therapeutics, University of Turku and Unit of Clinical Pharmacology, TYKSLAB, Turku, Finland, by using high-performance liquid chromatography and coulometric electrochemical detection (Scheinin *et al.* 1991). The lower limit of quantitation was 0.1 nmol/l and the intra- and inter-assay coefficients of variation were less than 10 % in the relevant concentration range.

4.7 Pharmacokinetic analysis

4.7.1 Noncompartmental pharmacokinetic analysis

In Studies I – III and V, the peak dexmedetomidine, H-3 or paracetamol concentrations in plasma (C_{max}) and the corresponding time points (t_{max}) were directly observed from the data. Consecutive values less than the lower limit of quantitation were treated in the subsequent statistical analysis as follows: The first value was treated as equal to 0.5 times the lower limit of quantitation, and the following values were treated as equal to zero. Areas under the dexmedetomidine plasma concentration–time curves with extrapolation to infinity ($AUC_{0-\infty}$) and areas under the paracetamol plasma concentration–time curves from 0 to 90 min ($AUC_{0-90\ min}$) were estimated by using the trapezoidal rule. In patients lacking data during the 48 hour follow-up period after stopping dexmedetomidine infusion in Study III, $AUC_{0-\infty}$ was estimated by using the mean k_e value of the other subjects as follows: $AUC_{0-\infty} = AUC_{0-last}$ + last measured concentration / mean k_e. The linear trapezoidal rule was used when successive concentration values were increasing and the logarithmic trapezoidal rule was used when successive concentration values were decreasing after the peak concentration. For each subject, the terminal log-linear phase of plasma drug concentration-time curve for post-infusion data was identified visually and an elimination rate constant (k_e) was determined by regression analysis. The elimination half-life ($t_{1/2}$) was calculated from the equation $t_{1/2} = \ln 2 / k_e$. Plasma clearance (Cl) and volume of distribution during elimination (V_z) or during steady-state (V_{ss}) were calculated by the use of standard non-compartmental methods based on statistical moment theory. During the continuous dexmedetomidine infusion, dexmedetomidine clearance at steady state, Cl_{ss} was repetitively estimated from $Cl_{ss} = I_{ss} / C_{ss}$, where I_{ss} = infusion rate at steady-state and C_{ss} = concentration at steady-state. It was estimated that steady state was reached after a constant infusion of 15 hours, which clearly exceeds the 3.3 half-lives generally assumed to be necessary for reaching steady state during dexmedetomidine infusions (Karol and Maze 2000, Rowland and Tozer 2011). The bioavailability of intranasally administered dexmedetomidine (F) was calculated as follows: $F = AUC_{0-\infty\ intranasal} / AUC_{0-\infty\ intravenous}$.

The haemodiafiltration clearance was calculated as follows:
Cl_{dial} (ml/min) = $Q_p \bullet (A_p-V_p)/A_p$, where Q_p is the plasma flow (ml/min) and A_p and V_p are concentrations of dexmedetomidine in arterial plasma entering and venous plasma leaving the dialyser. Q_p was calculated as follows: $Q_p = Q_b \bullet (1\text{-Hct})$, where Q_b is blood flow and Hct is the haematocrit value (%).

The pharmacokinetic data were analyzed with WinNonlin 4.1 and WinNonlin 5.0.1 Professional pharmacokinetic programs (Pharsight, Mountain View, CA, USA) in Studies I-II and Study III, respectively.

4.7.2 Population pharmacokinetic analysis

In Study IV, the time courses of the dexmedetomidine concentrations were analyzed by using a linear mamillary model with two or three compartments, using non-linear mixed effect modeling (NONMEM 7.1.2, ICON Development Solutions, Ellicott City, MD, USA). The pharmacokinetic models were parameterized using elimination and inter-compartmental (distributional) clearances and volumes of distribution. The inter-individual variability of the pharmacokinetic parameters was modeled by exponential random effects: $\theta_i = \theta_{POP} \cdot e^{\eta_i}$, where θ_i is the parameter value in the i^{th} subject, θ_{POP} is the population value of this parameter, and η is a random variable with a mean of zero and a variance of ω_i^2. The residual intra-individual variance was modelled by using a combined proportional and additive error model: $c_{mij} = c_{Pij} + c_{Pij} \cdot \varepsilon_{ij1} + \varepsilon_{ij2}$, where c_{mij} is the j^{th} measured concentration in the i^{th} subject, c_{pij} is the corresponding predicted value, and ε_1 and ε_2 are random variables with means of zero and variances of σ_1^2 and σ_2^2. The first order conditional estimates algorithm with η-ε interaction was used.

4.8 Pharmacodynamic assessment

4.8.1 Sedative effects

In Study I, the Maddox wing test was used to measure the effect of dexmedetomidine on the coordination of the extraocular muscles (Hannington-Kiff 1970), and the Bispectral Index (BIS) was used to monitor the level of sedation (Sigl and Chamoun 1994). Subjective effects were recorded with 100-mm horizontal visual analogue scales (VAS) with opposite qualities at each end (no effect of the drug/very strong effect of the drug, excellent performance/poor performance, alert/drowsy) (Bond and Lader 1974). For each variable, the area under the response-time curve (AUEC) was determined by using the trapezoidal rule in fractions of 0 to 0.5 and 0 to 3 hours. In Study III, the level of sedation was assessed with the Richmond Agitation-Sedation Scale RASS (Sessler *et al.* 2002).

4.8.2 Haemodynamic effects

In Studies I and IV, heart rate and systolic and diastolic blood pressure were measured to assess the haemodynamic effects of dexmedetomidine. In Study I, AUEC was determined by using the trapezoidal rule in fractions of 0 to 0.5, and 0 to 10 hours. In Study IV, haemodynamic data were averaged over periods of 6 minutes resulting in a time resolution of 0.1 hour. The mean (standard deviation) and the maximum relative increase and decrease for each variable in individual patients were determined during the 24 first hours of dexmedetomidine infusion.

4.8.3 Sympatholytic effects

In Study I, adrenaline and noradrenaline concentrations in plasma were measured to assess the sympatholytic effects of dexmedetomidine. For adrenaline and noradrenaline concentrations, the area under the concentration-time curve (AUC) was determined by using the trapezoidal rule in fractions of 0 to 0.5 and 0 to 3 hours.

4.8.4 Gastrointestinal effects

4.8.4.1 Gastric emptying

Paracetamol is not absorbed from the stomach but is rapidly absorbed from the small intestine. Consequently, the rate of gastric emptying determines the rate of absorption of orally administered paracetamol (Heading *et al.* 1973). The subjects were given orally 1.0 g of paracetamol (Panadol Forte®, GlaxoSmithKline Consumer Healthcare A/S, Copenhagen, Denmark) with 100 ml of tap water (25 °C) at t = 0 min. Venous blood samples were collected as indicated in Table 9 to determine plasma paracetamol concentrations. Gastric emptying was assessed by the rate of paracetamol absorption by using the time to peak plasma concentration, the peak plasma concentration and the area under the plasma concentration-time curve.

4.8.4.2 Oro-caecal transit time

Hydrogen is produced and exhaled when colonic bacteria ferment lactulose, an unabsorbable disaccharide. The time between ingestion of lactulose and an increase in exhaled hydrogen represents the oro-caecal transit time (Read *et al.* 1985, Eisenmann *et al.* 2008). The subjects were given per os 10 g of lactulose (Laktulos Merck NM® 667 mg/ml, Merck NM AB, Stockholm, Sweden) with 50 ml of tap water. The hydrogen concentration in exhaled air was measured with a hand-held device developed for this purpose (Gastro^{+} Gastrolyzer®, Bedfont Scientific Ltd, Rochester, Kent, UK) immediately before administration of lactulose (baseline) and thereafter at 15 min intervals, and the time between lactulose intake and the first occurrence of a sustained increase in exhaled hydrogen concentrations (i.e. an increase of > 10 ppm above baseline in at least three consecutive measurements) was taken as a measure of the oro-caecal transit time.

4.9 Assessment of safety and tolerability

4.9.1 Systemic effects in healthy volunteers

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 forms.

4.9.2 Local tolerability of intranasal dexmedetomidine

The tolerability of intranasally administered dexmedetomidine was assessed with visual analogue scales by the study subjects and by visual inspection of the nasal mucosa by the investigator immediately prior to administration (baseline) and thereafter at 1, 5 and 10 h. Subjective effects (no irritation/strong irritation, no obstruction/total obstruction, no numbness/total numbness, no rhinorrhea/strong rhinorrhea) were recorded by using VAS as described above. In the visual inspection by the investigator, possible local mucosal irritation, inflammation, bleeding and ulcerations were recorded. For each VAS value, AUEC was determined for 10 hours by using the trapezoidal rule.

4.9.3 Prolonged administration of high-dose dexmedetomidine in critically ill patients

In Study III, adverse events, heart rate, mean arterial blood pressure (MAP), 12-lead ECG, continuous ECG and safety laboratory assessments were used as safety and tolerability variables. Adverse events and serious adverse events were defined as suggested by the European Medicines Agency (European Medicines Agency 1995). In addition to clinically significant changes in vital signs, sustained MAP lower than 50 mmHg or higher than 125 mmHg and heart rate lower than 50 bpm or higher than 120 bpm (provided change in heart rate was $\geq$ 10%) were reported as adverse events.

Cardiac rhythm, including arrhythmias and atrioventricular blocks, was followed continuously and recorded daily. Any clinically significant new abnormalities since the last report were reported as adverse events. In addition, any changes indicative of myocardial ischaemia were reported as adverse events.

Blood samples were collected for complete blood count, glucose, urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, troponin T, total protein, triglycerides, total cholesterol, sodium, potassium, calcium, chloride and cortisol. Changes in the laboratory parameters resulting to a new diagnosis or a change in the treatment were considered to be clinically significant and were reported as adverse events. In addition, elevated troponin T indicative of myocardial ischaemia, liver enzymes > 5 times upper limit of normal and bilirubin > 5 times upper limit of normal were reported as adverse events.

4.10 Statistical analysis

4.10.1 General

The results are expressed as median (range), mean (coefficient of variation (%)) or geometric mean (coefficient of variation (%)), depending on the distribution of the parameter. In studies with comparators, Wilcoxon's signed rank test and Friedman's test followed by pairwise comparisons with Dunn's test with adjustment for multiple comparisons were used to compare the two or three phases, respectively. Differences were regarded as significant at $p < 0.05$ except in Study IV, where a more conservative significance level of $p < 0.01$ was used to consider multiple testing in assessing the goodness of fit of the population pharmacokinetic model.

Relationships of dexmedetomidine clearance and plasma creatinine, and the total dexmedetomidine dose and the dexmedetomidine $AUC_{0-\infty}$ were evaluated by using linear regression. Evaluation of the effects of infusion duration and infusion rate on dexmedetomidine clearance was done by using analysis of covariance. The effect of baseline patient factors on the pharmacokinetics of dexmedetomidine was tabulated by using descriptive statistics and analysed by patient factor. Continuous patient factors were dichotomised in descriptive tabulations using median as a cut-point. These patient factors included gender, age, Simplified Acute Physiology Score (SAPS II, (Le Gall *et al.* 1993)) at screening, and baseline heart rate, blood pressure, creatinine and creatinine clearance calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976). An analysis of variance model (for categorical factors) and analysis of co-variance (for continuous factors) were used to assess statistical significance. In these analyses, no multiplicity adjustments were done.

The data were analysed by using statistical programs PASW Statistics 18.0 for Mac (SPSS Inc, Chicago, IL, USA); R (R Development Core Team (2010), R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org); SAS 9.2 (SAS Institute Inc, Cary, NC, USA); and NONMEM 7.1.2 (ICON Development Solutions, Ellicott City, MD, USA) in Study I, II, III and IV, respectively.

4.10.2 Goodness of fit of the population pharmacokinetic model

$$PE_{ij} = \frac{Cm_{ij} - Cp_{ij}}{Cp_{ij}}$$

Goodness of fit was judged by residual plots, by the objective function value (OFV) which is minimized in the fitting procedure, and by the median prediction errors, MDPE = median$\{PE_{ij}\}$ and MDAPE = median$\{|PE_{ij}|\}$, where PE_{ij} is the prediction error. Statistical comparison of the two models was performed by using the difference of the objective function value (ΔOFV). In order to consider multiple testing, a more conservative significance level of $p < 0.01$ corresponding to $\Delta OFV > 6.6$ for one degree of freedom was used.

4.10.3 Covariate analysis

In Study IV, the effects of subject age, sex, body mass, height, body mass index and lean body mass on dexmedetomidine pharmacokinetics were evaluated. Additionally, the effects of cardiac output, plasma bilirubin and albumin concentrations, PaO_2/FiO_2 and renal replacement therapy were investigated. Renal function was assessed by estimating the glomerular filtration rate (GFR) from plasma creatinine concentrations, using the Cockcroft-Gault formula (Cockcroft and Gault 1976).

First, the model was estimated without any covariates. The individual Bayesian estimates of the model parameters were plotted against the covariates and assessed for a covariate influence using linear regression. Covariates with an effect on a model parameter were then included step by step in the model, by using a linear relationship which was centered around the median value of the covariate:

$$\theta_i = \hat{\theta} \cdot (1 + \theta_{cov} \cdot \frac{COV_i - COV_{median}}{COV_{median}}),$$

where $\hat{\theta}$ is the value of the parameter θ in the "average" patient with a covariate value equal to the median value COV_{median} of the studied individuals. COV_i denotes the individual value of the covariate and θ_{cov} is the covariate parameter that quantifies the magnitude of the covariate effect. For those covariates with multiple measurements within a subject (albumin concentration, GFR, PaO_2/FiO_2, cardiac output, plasma bilirubin) each measurement was used in the modeling assuming a stepwise change, i.e. that the value remained constant between two measurements. A covariate effect was assumed to be significant if the OFV was significantly improved, and if the 95 % confidence interval of θ_{cov} did not include zero. After the full model with all covariate effects was developed, each covariate effect was tested again for significance by fixing the corresponding parameter $\theta_{cov} = 0$.

4.10.4 Validation and simulations of the population pharmacokinetic model

For model validation and for obtaining nonparametric 95 % confidence intervals of the model parameters, bootstrap analysis with 1000 replicates (by subject with replacement) was performed. To illustrate the covariate effects, the time for a 50 % concentration decrement after the termination of the continuous drug infusion (context-sensitive half-time (Hughes *et al.* 1992)) was estimated for fictive subjects having different covariate values, based on the 25%, 50% and 75% quartiles of the covariate distributions within the study population. In order to compare the results with those of previous studies, the context-sensitive half-time was further estimated for a typical subject of this study population (age 60 years, albumin concentration 14 g/l, height 174 cm) using pharmacokinetic models of dexmedetomidine reported in the literature (Dyck *et al.* 1993a, Talke *et al.* 1997, Venn *et al.* 2002, Lin *et al.* 2011).

4.11 Study monitoring

Studies I and II underwent limited external monitoring by a qualified representative of Turku Clinical Research Centre. In study III, there was an external monitor of the sponsor of the study who ensured that the study complied with good clinical practice guidelines and applicable regulatory requirements. Additionally, the monitor verified that the protocol was followed in all aspects and that data were recorded accurately. In Study IV, there was no external monitoring.

5 RESULTS

5.1 Dexmedetomidine pharmacokinetics in healthy volunteers

The median (range) plasma concentrations of dexmedetomidine after intranasal and intravenous administration are shown in Figure 3, and the calculated pharmacokinetic parameters are shown in Table 10. The values of C_{max} were 0.34 (0.23-0.70) and 3.48 (2.70-3.72) ng/ml after intranasal and intravenous administration, respectively. The median value for t_{max} was 38 (15-60) min after intranasal administration. The corresponding values for $t_{½}$ were 114 (107-151) and 115 (99-145) min and for dexmedetomidine $AUC_{0-\infty}$ 74.1 (45.7-114.4) and 123.6 (92.2-138.4) min·ng/ml. The number of subjects having dexmedetomidine concentrations below the lower limit of quantitation was one at 8 h and five at 10 h following intravenous dexmedetomidine. Following intranasal dexmedetomidine, the corresponding numbers were two at 8 h and four at 10 h, respectively. Dexmedetomidine concentrations could be quantitated in all other samples drawn after the administration of dexmedetomidine. The median absolute bioavailability of intranasal dexmedetomidine was 65 %, although the individual values had notable variation, ranging from 35 to 93 %.

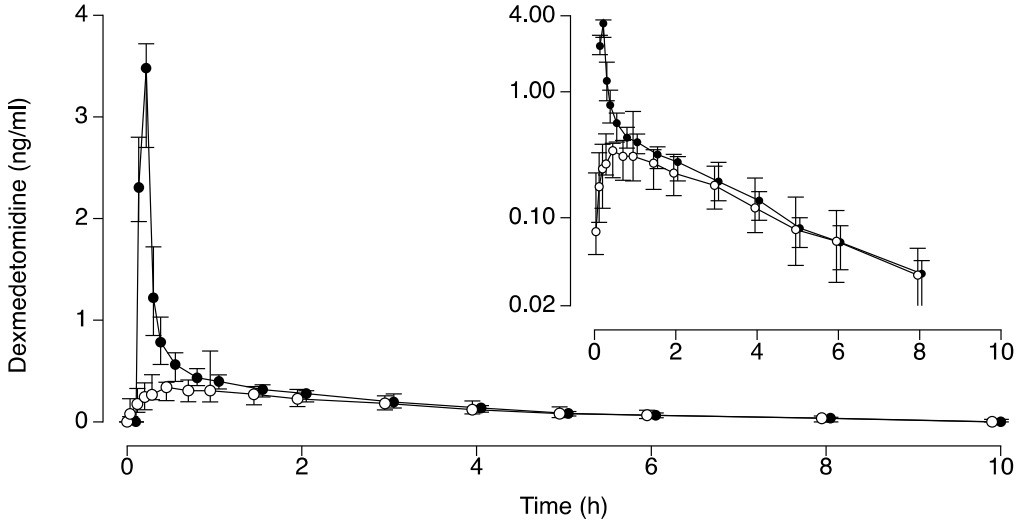


Figure 3. *Dexmedetomidine concentrations in plasma (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers. The concentrations are shown both on arithmetic and logarithmic scales (inset).*

Table 10. Pharmacokinetic parameters after 84 μg of dexmedetomidine administered intravenously and intranasally in six healthy male volunteers.

Subject No	1	2	3	4	5	6	Median	Range
Intravenous administration								
BMI (kg/m^2)	22.8	24.8	26.5	25.9	25.9	19.6	25.3	19.6 - 26.5
C_{max} (ng/ml)	3.26	3.72	3.69	2.70	3.36	3.60	3.48	2.70 - 3.72
$t_{½}$ (min)	103	126	131	145	99	104	115	99 - 145
$AUC_{0-\infty}$ (ng min/ml)	129	136	138	110	92.2	118	124	92.2 - 138
Extrapolated AUC (%)	3.5	5.7	3.2	8.0	6.0	2.7	4.6	2.7 - 8.0
Cl (l/h)	39.0	37.2	36.4	45.7	54.7	42.7	40.9	36.4 - 54.7
V_{ss} (l)	73.2	87.2	86.1	120	94.7	80.1	86.6	73.2 - 120
Intranasal administration								
C_{max} (ng/ml)	0.23	0.28	0.70	0.37	0.31	0.46	0.34	0.23 - 0.70
t_{max} (min)	15	60	60	45	30	20	38	15 - 60
$t_{½}$ (min)	109	151	118	109	107	141	114	107 - 151
$AUC_{0-\infty}$ (ng min/ml)	45.7	71.8	114	76.3	56.7	110	74.1	45.7 - 114
Extrapolated AUC (%)	10.6	7.2	3.5	5.4	8.9	10.6	8.1	3.5 - 10.6
F (%)	35.3	53	82.6	69.2	61.5	93.3	65.4	35.3 - 93.3

BMI, body mass index; C_{max}, peak plasma concentration; $t_{½}$, elimination half-life; $AUC_{0-\infty}$, area under dexmedetomidine plasma concentration–time curve; Extrapolated AUC, fraction of AUC extrapolated; Cl, plasma clearance; V_{ss}, steady-state volume of distribution; t_{max}, time corresponding to C_{max}; F, bioavailability.

5.2 Dexmedetomidine pharmacokinetics in intensive care patients

A total of 13 and 21 intensive care patients were screened and included in Studies III and IV, respectively. The measured dexmedetomidine concentrations are depicted in Figure 4.

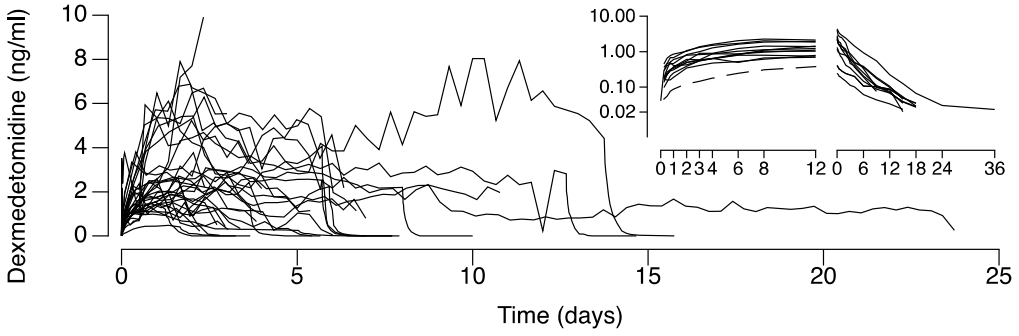


***Figure 4**. Measured dexmedetomidine concentrations in 34 intensive care patients (main figure), and concentration profiles during the initial 12-hour constant rate infusion (n = 13) and the 48-hour follow-up after stopping the infusion (n = 10, inset). During the constant rate phase, the infusion rate was 0.7 μg/kg/h in all but one patient, who received dexmedetomidine 0.1 μg/kg/h (dashed line).*

5.2.1 Noncompartmental pharmacokinetics

In Study III, the observed dexmedetomidine concentrations varied widely between the 13 patients. The values of the pharmacokinetic variables are shown in Table 11. The geometric mean value of dexmedetomidine clearance was 39.7 l/h (40.9%). In the 10 patients with complete data sets, the geometric mean values for $t_{½}$, Cl and V_z during the elimination phase were 3.7 h (38.1%), 41.4 l/h (46.7%) and 223.3 l (35.3%), respectively.

There were altogether 116 steady-state concentrations in 12 subjects (Figure 5). Fifteen of the steady-state concentrations were reached during an infusion rate of 0.1 µg/kg/h, one during an infusion rate of 0.4 µg/kg/h, three during an infusion rate of 0.7 µg/kg/h, one during an infusion rate of 2.1 µg/kg/h, and 96 during an infusion rate of 2.5 µg/kg/h. The geometric mean value for Cl_{ss} was 53.1 l/h (CV 54.8 %, range 8.4 to 115 l/h). There was a statistically significant relationship between dexmedetomidine Cl_{ss} and the duration of the infusion (p = 0.0007) and infusion rate (p < 0.0001) in univariate analysis. In multivariate analysis, where both the duration of the infusion and infusion rate were included in the model, only infusion rate was statistically significantly correlated with dexmedetomidine Cl_{ss} (p < 0.001). The interaction between the duration of the infusion and the infusion rate was not statistically significant. In Study V, the dose rate of dexmedetomidine remained constant for relatively long periods of time during three separate intervals. The calculated clearance was 55 l/h, 92 l/h and 87 l/h during the 2nd to 6th, 14th to 20th and 21st to 23rd day of the dexmedetomidine infusion, respectively.

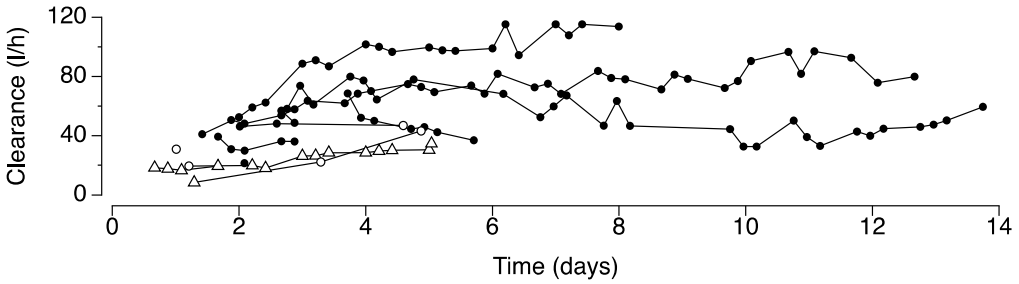


Figure 5. *Dexmedetomidine clearance at 116 steady-states defined by a 15-hour constant rate infusion in 12 subjects. Open triangles, open circles and closed circles indicate infusion rate of 0.1, 0.4 – 2.1 and 2.5 µg/kg/h, respectively. Each line represents one patient. In two patients, only one steady-state was achieved, and the corresponding clearances are depicted with a single symbol.*

Table 11. Characteristics and pharmacokinetic parameters of dexmedetomidine infusions in 13 intensive care patients.

	Patient														
Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Mean**	**CV (%)**
Rate of the 12-hour initial infusion (μg/kg/h)	0.1	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.6*	58.1
Maximum infusion rate (μg/kg/h)	0.1	2.1	2.5	2.5	2.5	2.5	2.5	0.95	0.7	2.5	1.2	2.5	2.5	1.5*	117
Length of infusion (h)	40	142	137	88	55	304	137	30	121	330	13	72	192	92.0*	117
Cumulative dose (mg)	0.34	11	25	8.7	8.0	56	17	1.4	2.4	82	1.1	13	46	21.0	120
$AUC_{0-\infty}$ (ng h/ml)	17.8	376	550	174	252	924	337	39.0	100	1530	29.7	350	583	213*	233
Extrapolated fraction of $AUC_{0-\infty}$ (%)	1.3	0.1	0.0	0.1	22.0	0.0	0.0	0.6	0.2	0.0	37.1	9.3	0.0		
$t_{½}$ (h)	4.5	4.2	2.9	5.0	-	2.4	3.4	3.3	6.9	5.1	-	-	2.1	3.7 *	38.1
Cl (l/h)	18.9	30.4	45.4	50.4	31.8	60.7	51.5	35.5	23.7	53.7	36.1	36.7	79.0	39.7*	40.9
V_z (l)	123	184	193	362	-	213	252	170	234	391	-	-	234	223*	35.3

*Due to missing samples for subjects 5, 11 and 12, it was not possible to define the elimination phase parameters for these subjects, and the area under the dexmedetomidine concentration time curve extrapolated to infinity ($AUC_{0-\infty}$) was estimated by using the mean elimination half-life of the other patients. Subject 5 received haemodiafiltration. CV, coefficient of variation; * geometric mean; $t_{½}$, elimination half-life; Cl, plasma clearance; V_z, volume of distribution during elimination.*

$AUC_{0-\infty}$ of dexmedetomidine plotted against the total cumulative dose is shown in Figure 6. There was a statistically significant linear relationship ($r^2 = 0.95$; $p < 0.001$) between $AUC_{0-\infty}$ and cumulative dose of dexmedetomidine.

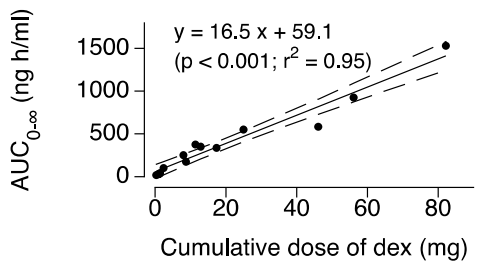


***Figure 6**. Relationship of the total dexmedetomidine dose and the area under the dexmedetomidine concentration-time curve extrapolated to infinity (AUC). The dashed lines represent the 95% confidence intervals for the regression line (solid line). Dex, dexmedetomidine.*

Dexmedetomidine Cl was higher (p = 0.006) in patients with low baseline SAPS II scores (< 42) compared to subjects with high scores (≥ 42). The corresponding values for geometric mean Cl were 57.6 l/h (24.7%) and 33.2 l/h (43.5%), respectively. In subjects with low baseline SAPS II scores (< 42), dexmedetomidine $t_{1/2}$ (h) was shorter (p = 0.036) compared to subjects with higher baseline SAPS II scores (≥ 42), with geometric mean values being 2.9 h (CV 39.9%) and 4.4 h (27.6%), respectively. Dexmedetomidine Cl and creatinine clearance showed a linear correlation at baseline (p = 0.026). Other patient factors did not significantly affect clearance.

5.2.2 Multicompartmental analysis

In Study IV, a total of 534 blood samples were drawn from 21 ICU patients for determination of dexmedetomidine concentrations. The geometric mean of the infusion duration was 101 (CV 77%) hours, dexmedetomidine dose 1.14 (39%) μg/kg/h and maximum dexmedetomidine dose 1.62 (39%) μg/kg/h. A two-compartment model was adequate to describe the pharmacokinetics of dexmedetomidine. A three-compartment model yielded only a slightly better fit (ΔOFV = 12.3, p = 0.015) with large standard errors and large inter-individual variances.

5.2.2.1 Covariate effects

The covariates of patient body weight, height, body mass index, lean body mass and sex had no significant effects on dexmedetomidine pharmacokinetics. Only eight patients had sufficient data for the assessment of the effect of cardiac output (CO) on the model. As dexmedetomidine itself reduces CO (Dutta *et al.* 2000), the normalized measured cardiac output

$$RCO = CO/CO_{baseline}$$

was plotted against the corresponding measured dexmedetomidine concentra-

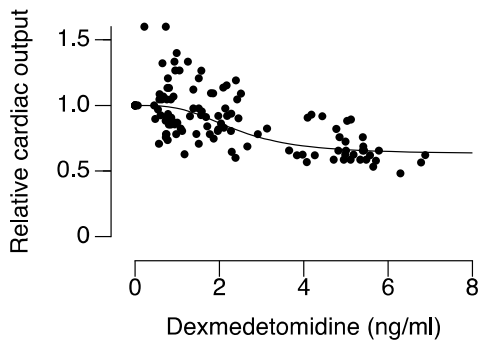


***Figure 7**. Baseline-normalized relative cardiac output (baseline = 1) vs. measured dexmedetomidine concentration. The solid black line shows the prediction of the sigmoid model, fitted to the data.*

tion (Figure 7), and a sigmoid function was fitted to the data by population analysis:

$$RCO = 1 - 0.37 \cdot \frac{C^{3.15}}{C^{3.15} + 2.40^{3.15}}$$

For those patients without CO measurements, estimates of RCO were calculated for each measured dexmedetomidine concentration using this formula. Dexmedetomidine clearance significantly decreased with decreasing RCO, and a nonlinear relationship described best the cardiac output effect on clearance:

$$Cl = \hat{Cl} \cdot RCO^{\theta_5}$$

($\Delta OFV = 142.9$, $p < 0.0001$).

Dexmedetomidine clearance decreased with age (Figure 8, $\Delta OFV = 6.9$, $p = 0.009$), whereas the other parameters did not show significant age effects. Dexmedetomidine clearance also decreased slightly with decreasing GFR. However, age and GFR are strongly intercorrelated as the formula used to estimate GFR includes age. Therefore, only age but not GFR were used as a covariate for clearance.

The volume of distribution at steady state, V_{SS}, showed a significant increase with decreasing albumin concentrations (Figure 8, $\Delta OFV = 9.7$, $p = 0.002$), whereas the other parameters did not show significant albumin effects. V_{ss} also increased with decreasing PaO_2/FiO_2, but as the albumin concentration and PaO_2/FiO_2 were positively associated ($r = 0.70$), only the albumin concentration was used as a covariate for V_{ss}. Plasma bilirubin concentrations had no significant influence on dexmedetomidine pharmacokinetics.

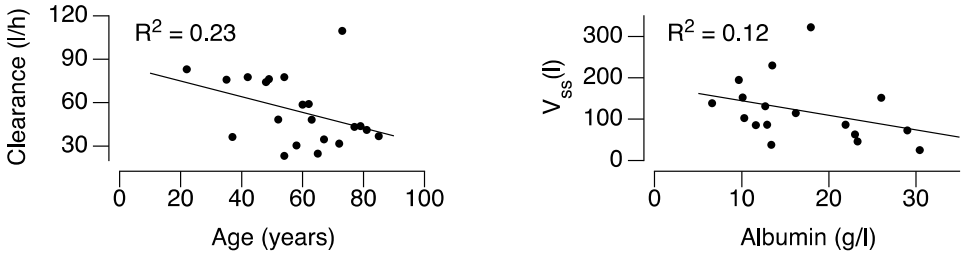


Figure 8. *Scatter plots of the individual Bayesian estimates of clearance vs. age and of volume of distribution at steady-state vs. albumin concentration. Each data point represents one patient. In four patients, no albumin concentrations were available. Multiple albumin concentration measurements within one subject were averaged. The solid black line was obtained by linear regression analysis, R^2 is the corresponding regression coefficient.*

Thus, the final pharmacokinetic model was as follows:

$$\mathrm{Cl} = \theta_1 \cdot (1 + \theta_6 \frac{\mathrm{age} - 60}{60}) \cdot \mathrm{RCO}^{\theta_5}$$
$$\mathrm{Q} = \theta_2$$
$$\mathrm{V_1} = \theta_3$$
$$\mathrm{V_{ss}} = \theta_4 \cdot (1 + \theta_7 \frac{\mathrm{albumin} - 14}{14})$$

with the albumin concentration measured in g/l. The parameter estimates for this final model are summarized in Table 12, and the measured concentrations vs. the individual and population predictions are depicted in Figure 9. For the average patient of this study, the half-lives of dexmedetomidine (95 % CI) were $t_{1/2\alpha}$ = 2.0 (1.2–2.8) min, and $t_{1/2\beta}$ = 122 (86–192) min. Comparing the final model with the simple two-compartment model without any covariates, the median prediction error (MDPE) decreased from -5.9 % to -3.7 %, and the median absolute prediction error (MDAPE) decreased from 33.5 % to 21.7 %.

Table 12. Results of the population pharmacokinetic modelling**.**

Variable	Estimate	Standard error	Bootstrap median	Bootstrap 95 % CI
Population parameters				
$\theta_1 = \hat{\mathrm{Cl}}$ (l/h)	57.0	5.5	57.4	(42.1, 65.6)
$\theta_2 = \hat{\mathrm{Q}}$ (l/h)	183	13	191	(157, 212)
$\theta_3 = \hat{\mathrm{V}}_1$ (l)	12.3	1.7	12.0	(7.6, 17.0)
$\theta_4 = \hat{\mathrm{V}}_{ss}$ (l)	132	20	128	(96, 189)
Covariate effects				
θ_5 (cardiac output on Cl)	1.24	0.38	1.15	(0.34, 1.90)
θ_6 (age on Cl)	-0.78	0.24	-0.73	(-1.26, -0.18)
θ_7 (albumin on V_{ss})	-0.51	0.02	-0.51	(-0.72, -0.07)
Inter-individual variability				
Cl (%)	33.5	5.8	32.0	(21.7, 44.9)
Q (%)	25.1	5.2	23.9	(0.3, 35.5)
V_1 (%)	53.4	11.4	51.6	(30.2, 80.5)
V_{ss} (%)	65.0	9.8	60.7	(44.3, 80.9)
Residual variability				
Additive (ng/ml)	0.017	0.003	0.017	(0.001, 0.025)
Proportional (%)	16.0	1.6	15.9	(12.9, 18.5)

95 % CI, 95 % confidence interval; Cl, total body clearance; Q, inter-compartmental clearance; V_1, central volume of distribution; V_{ss}, steady state volume of distribution.

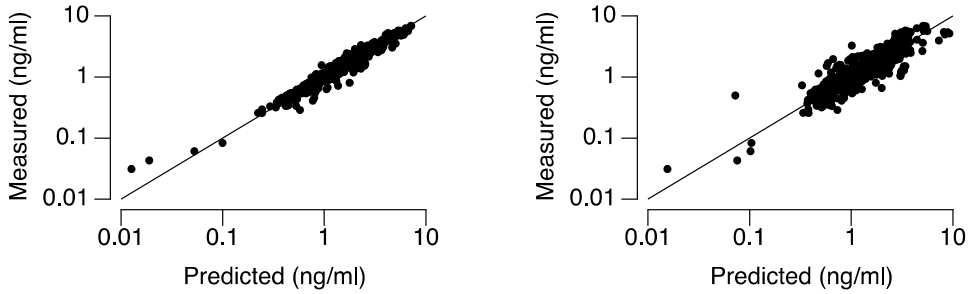


Figure 9. *Measured dexmedetomidine concentrations vs. the individual Bayesian predictions (left) and the population predictions (right), as obtained with the final pharmacokinetic model. The solid black line is the line of identity (measured = predicted).*

5.2.2.2 Simulations

The pharmacokinetic parameters and the context-sensitive half-time for fictive subjects of different ages and having different albumin concentrations were simulated to illustrate covariate effects. The elimination half-life and the context-sensitive half-life of dexmedetomidine were increased in elderly patients and also in patients with a low albumin concentration (Table 13 and Figure 10).

Simulations of the context-sensitive half-times for a typical subject calculated with the final pharmacokinetic model of this study and with pharmacokinetic models from the literature yielded similar results for the different models, with the exception of the model by Dyck (Dyck *et al.* 1993a), which predicted a much longer context-sensitive half-time (Figure 10).

Table 13. Patient characteristics used for simulation of context-sensitive half-life.

Characteristics	Age (years)	Albumin (g/l)	Cl (l/h)	V_{ss} (l)	$t_{1/2\beta}$ (min)
average age; average albumin	60	14	57.0	132	122
younger; average albumin	40	14	71.8	132	102
elderly; average albumin	80	14	42.2	132	155
average age; lower albumin	60	10	57.0	151	140
average age; higher albumin	60	20	57.0	103	94

Cl, total body clearance; V_{ss}, steady state volume of distribution; $t_{1/2\beta}$, elimination half-life.

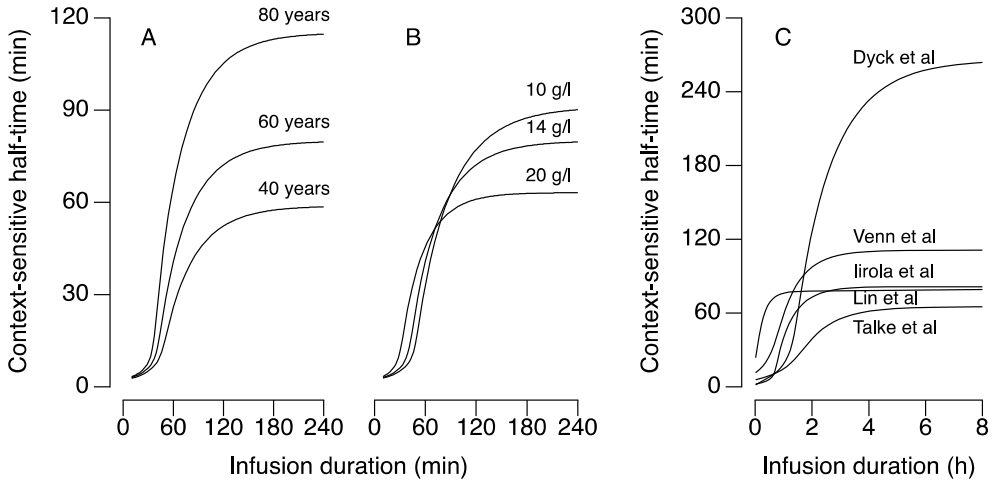


Figure 10. *Simulations of the time for a 50 % concentration decrement after termination of a continuous drug infusion (context-sensitive half-time) for fictive subjects having A) different age and an equal plasma albumin concentration of 14 g/l, B) different albumin concentration and an equal age of 60 years (see Table 13), and C) for a typical subject of this study (age 60 years, albumin concentration 14 g/l, height 174 cm) using the pharmacokinetic models of Study IV and the studies by Lin (Lin et al. 2011), Dyck (Dyck et al. 1993a), Talke (Talke et al. 1997) and Venn (Venn et al. 2002).*

5.2.3 Effect of renal replacement therapy

In Studies III and IV, altogether four patients received renal replacement therapy with haemodialysis or haemodiafiltration. Based on simultaneously measured drug concentrations in the afferent and efferent limbs of the filter circuit (n=1, Table 14) and population pharmacokinetic modelling (n=3), there was no evidence that dexmedetomidine was extracted from plasma by renal replacement therapy.

Table 14. Dexmedetomidine concentrations and haemodiafiltration clearance.

Sampling time point (hours)	A_p (ng/ml)	V_p (ng/ml)	Clearance (ml/min)
2	1.21	0.78	36.25
4	1.43	1.28	10.70
6	1.56	1.70	-9.15
8	1.67	1.64	1.83

A_p, dexmedetomidine concentration in arterial plasma entering the dialyser; V_p, dexmedetomidine concentration in venous plasma leaving the dialyser.

5.3 H-3 metabolite pharmacokinetics in intensive care patients

In Study III, the geometric mean value for $t_{½}$ of H-3 during the elimination phase was 9.1 h (CV 37.0%, n = 10). The geometric mean ratio of $AUC_{0-\infty}$ of H-3 metabolite to that of dexmedetomidine was 1.47 (105 %) ranging from 0.29 to 4.4. The ratio was not statistically significantly related to the total dose of dexmedetomidine (p = 0.528) or the duration of the infusion (p = 0.872).

5.4 Pharmacological effects of dexmedetomidine

5.4.1 Sedative effect in healthy volunteers

Subjective sedative effects of dexmedetomidine (drug effect, performance and drowsiness) and BIS results are shown in Figure 11. After intravenous administration of dexmedetomidine, drug effects became apparent sooner compared to intranasal application: $AUEC_{0–30\ min}$ values of subjective effects, BIS and the Maddox wing test were significantly ($p < 0.05$) different after intranasal and intravenous administration but there were no differences in the $AUEC_{0-3\ h}$ values.

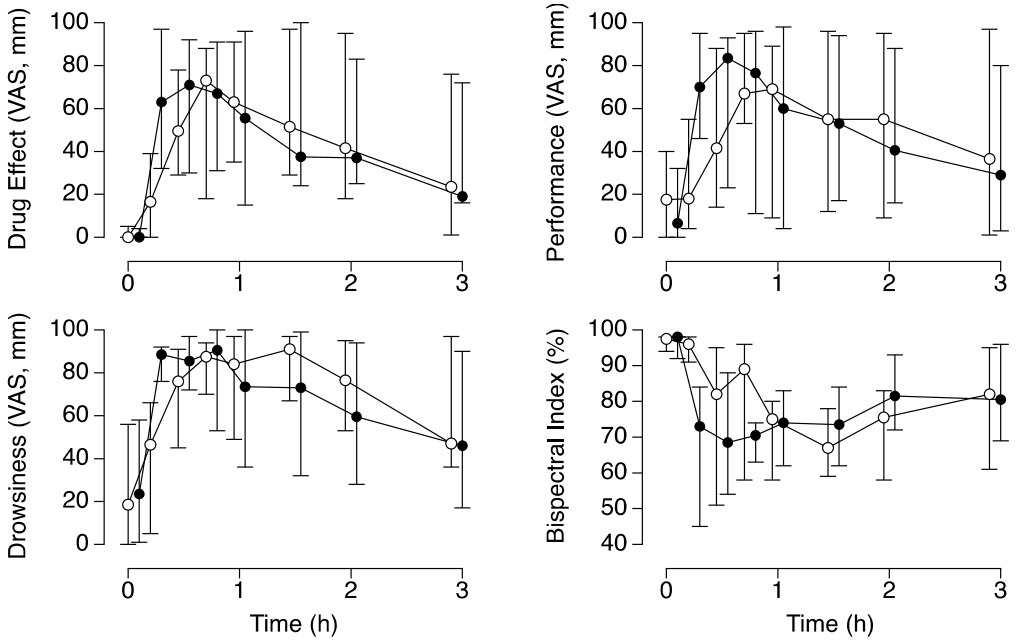


Figure 11. *Results (median (range)) of recordings of subjective effects (drug effect, performance, drowsiness) from visual analog scales (VAS) and Bispectral Index after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers.*

5.4.2 Sedative effect in intensive care patients

In Study III, altogether 88 RASS values were recorded in the 13 patients. In four of the 88 recordings (4.5 %), under-sedation was discovered, when the patients were treated according to the protocol (dexmedetomidine infusion enhanced with propofol infusion or boluses). All but one patient (12/13) needed at least one bolus dose of propofol to keep the RASS value in the target zone, and the median amount of propofol was 1869 mg/day (range 79-8505). The numbers of patients over-sedated, on target and under-sedated during the study are shown in Figure 12.

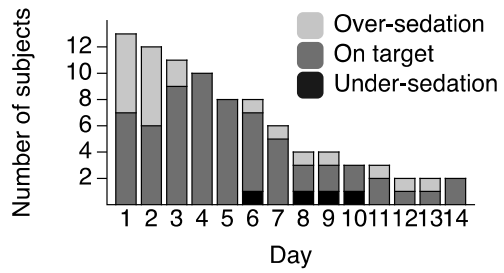


Figure 12. *Success in reaching the target Richmond Agitation-Sedation Scale in 13 intensive care patients receiving dexmedetomidine enhanced with propofol as rescue medication.*

5.4.3 Haemodynamic effects in healthy volunteers

In Study I, heart rate and systolic and diastolic blood pressure were monitored until 10 hours to assess the effects of dexmedetomidine. Based on the values for the area under the response-time curve (AUEC), heart rate was significantly ($p = 0.046$) lower during the initial 0-30 min period after intravenous than intranasal administration, but there was no statistically significant difference over the 0-10 hour period (Figure 13). Systolic and diastolic blood pressures were similar regardless of the administration route and no statistically significant differences between the treatments were noted (Figure 14).

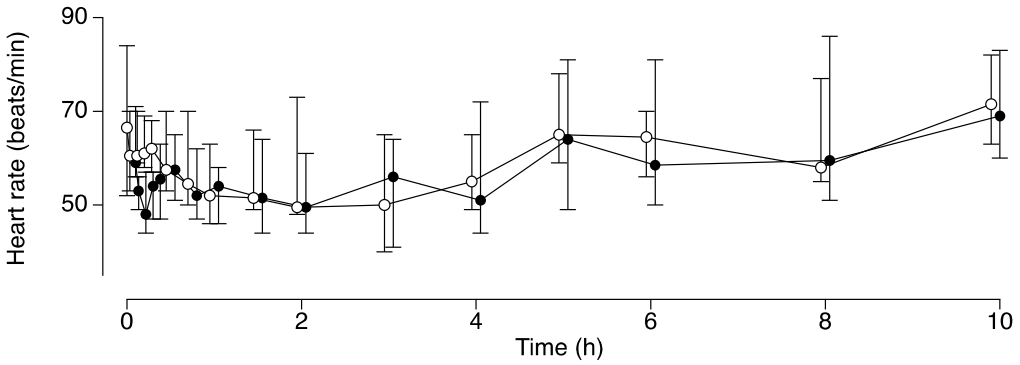


Figure 13. *Heart rate (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers.*

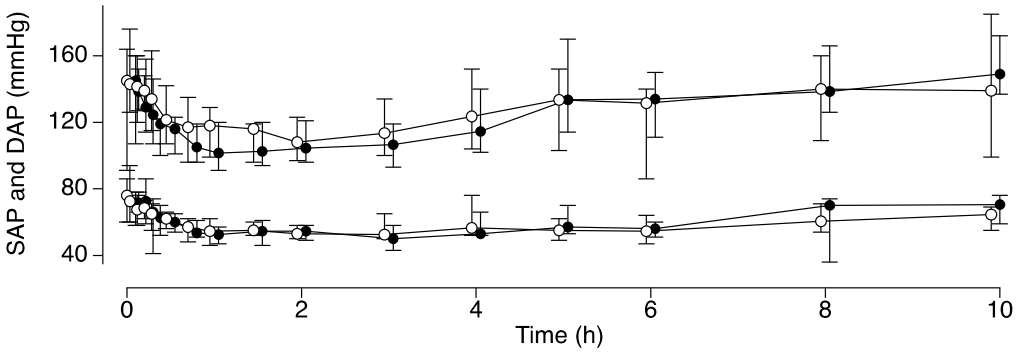


Figure 14. *Blood pressure (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers. SAP, systolic arterial pressure; DAP, diastolic arterial pressure.*

5.4.4 Haemodynamic effects in intensive care patients

During the first 24 h of dexmedetomidine infusion, the average heart rate decreased, whereas the mean systolic and diastolic blood pressure remained constant throughout the study (Figure 15). The maximum decrease and increase of heart rate in an individual patient (mean (SD)) was 32(16) % and 37(43) %, respectively. The maximum decreases and increases of systolic blood pressure in an individual patient were 29(11) % and 41(21) %, respectively. The maximum decreases and increases of diastolic blood pressure in an individual patient were 28(11) % and 39(19) %, respectively.

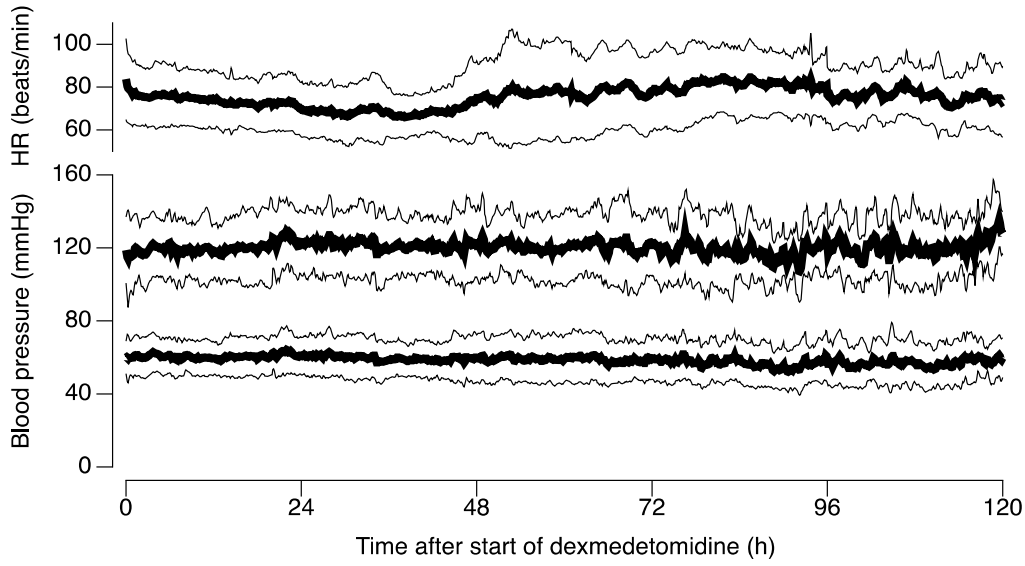


Figure 15*. Time courses of heart rate, and of systolic and diastolic blood pressure during dexmedetomidine infusion. Data are shown as mean (SD). HR, heart rate.*

5.4.5 Sympatholytic effects in healthy volunteers

There were no differences in plasma adrenaline concentrations between intravenous or intranasal administration routes as judged from values for $AUC_{0\text{-}30\ min}$ and $AUC_{0–3\ h}$. Plasma noradrenaline $AUC_{0–30\ min}$ was significantly lower ($p = 0.028$) after intravenous administration than after intranasal administration, but the values for $AUC_{0–3\ h}$ did not differ (Figure 16).

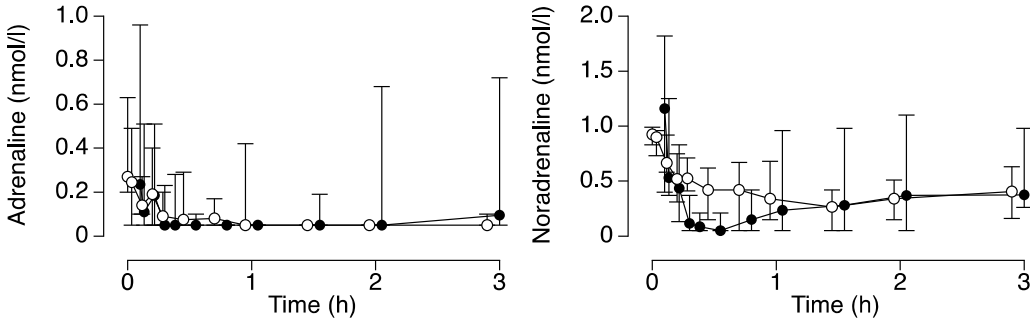


Figure 16. *Adrenaline and noradrenaline concentrations in plasma (median (range)) after administration of 84 µg of dexmedetomidine intravenously (closed circles) or intranasally (open circles) to six healthy male volunteers.*

5.4.6 Gastrointestinal effects in healthy volunteers

Median concentrations of paracetamol in plasma during the three phases of the study are shown in Figure 17. Individual times to reach the maximum concentration of paracetamol in plasma, maximal concentration values, areas under the plasma paracetamol concentration-time curves ($AUC_{0–90\ min}$) and oro-caecal transit times are depicted in Figure 18.

The time to reach the maximum concentration of paracetamol in plasma was significantly longer, the maximal observed paracetamol concentrations were significantly lower, the values of $AUC_{0–90\ min}$ were significantly smaller, and the oro-caecal transit times were significantly longer during the dexmedetomidine

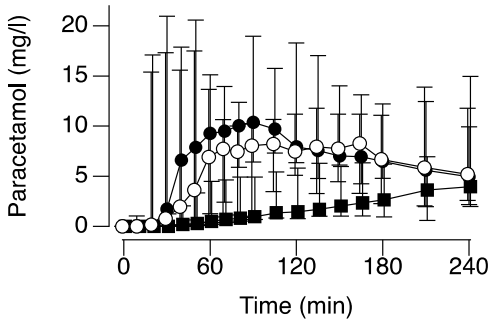


Figure 17*. Plasma concentrations of paracetamol (median (range)) in 12 healthy male volunteers after ingestion of 1 g of paracetamol and 10 g of lactulose following intravenous infusions of placebo (closed circles), dexmedetomidine (closed squares) and morphine (open circles).*

infusion than during the morphine and placebo phases (Table 15). No statistically significant differences were observed in these parameters between the placebo and morphine phases.

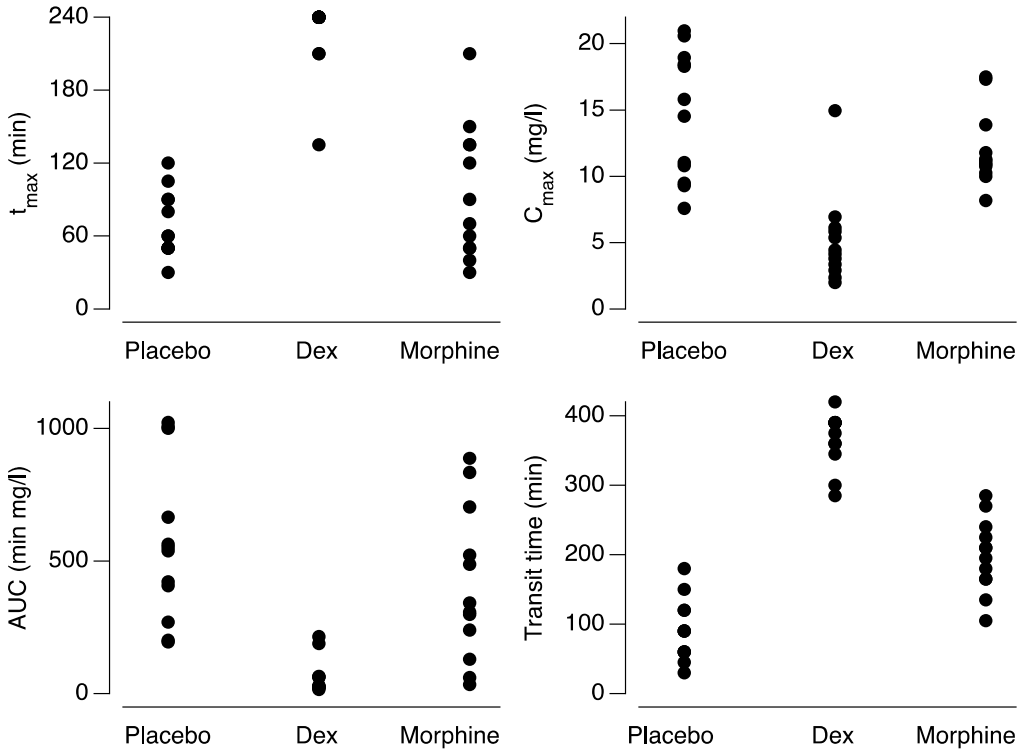


***Figure 18**. Individual values for the time to peak plasma paracetamol concentration (t_{max}), the peak plasma paracetamol concentration (C_{max}), the area under the paracetamol plasma concentration-time curve from 0 to 90 min (AUC) and the oro-caecal transit time measured by the hydrogen breath test in 12 healthy male volunteers after ingestion of 1 g of paracetamol and 10 g of lactulose following intravenous infusions of placebo, dexmedetomidine and morphine. Dex, dexmedetomidine.*

Table 15. Effects of intravenous dexmedetomidine and morphine on the gastrointestinal absorption of 1 g of oral paracetamol and oro-caecal transit time.

Variable	Placebo	Dexmedetomidine	Morphine
t_{max} (min)	60 (30-120)***	240 (135-240)	80 (30-210)**
C_{max} (mg/l)	15.2 (7.6-21.0)***	4.3 (2.0-15.0)	11.1 (8.2-17.5)*
$AUC_{0\text{-}90\ min}$ (min mg/l)	545 (195-1022)***	29 (15-215)	325 (34-887)*
Transit time (min)	90 (30-180)***	383 (285-420)	203 (105-285) *

**Significantly ($p < 0.05$) different from dexmedetomidine; **Significantly ($p < 0.01$) different from dexmedetomidine; ***Significantly ($p < 0.001$) different from dexmedetomidine.*

5.5 Concomitant treatments

There were no concomitant treatments in Studies I and II. Concomitant treatments were analysed in Studies III and Study V. In Study III, the most commonly used treatments during dexmedetomidine infusion were short-acting insulin (13/13), oxycodone (13/13), noradrenaline (13/13), rescue propofol (12/13), enoxaparin (12/13), esomeprazole (12/13) and beta-lactam antibacterials (11/13). None of the drugs used are known to be strong inhibitors or inducers of the enzymes relevant in the pharmacokinetics of dexmedetomidine.

5.6 Safety of dexmedetomidine administration

5.6.1 Systemic effects of dexmedetomidine in healthy volunteers

No adverse effects were detected, and no concomitant treatment was needed.

5.6.2 Local tolerability of intranasal dexmedetomidine

There were no visual signs of local mucosal irritation, inflammation, bleeding or ulceration of the nasal mucosa after intranasal administration of dexmedetomidine. In addition, no subjective adverse events were reported.

5.6.3 Prolonged administration of high-dose dexmedetomidine in critically ill patients

A total of 53 adverse events were reported in 12 subjects after the start of the study treatment in Study III. The most common adverse events were tachycardia (9 events), hypotension (5 events) and hypertension (4 events). Four of the adverse events were assessed as being related to the study treatment, namely three episodes of bradycardia and one episode of first degree atrioventricular block. These four adverse events were all resolved, the bradycardias requiring dexmedetomidine dose reduction, and, in two cases, administration of atropine and glycopyrrolate. Most of the adverse events were recorded in the highest dose range of 1.4 - 2.5 μg/kg/h, but there was no clear correlation between the onset of the adverse events and the dexmedetomidine concentration in plasma.

Twenty of the 53 adverse events, reported in 7 of the 13 subjects, were classified as serious. Five of the serious adverse events resulted in death, with three of the deaths occurring during the study drug infusion period and leading to withdrawal from the study treatment. The causes of the deaths were chronic pulmonary disease (n=2), sepsis, myocardial infarction with a myocardial rupture and pancreatitis.

6 DISCUSSION

6.1 Intranasal pharmacokinetics of dexmedetomidine in healthy volunteers

Bioavailability of orally and buccally administered dexmedetomidine has been described previously (Anttila *et al.* 2003), but the bioavailability after intranasal administration has remained unknown. However, intranasal dexmedetomidine has been used successfully as premedication in children (Yuen *et al.* 2008, Yuen *et al.* 2010) and for sedation in dental surgery (Cheung *et al.* 2011).

The average bioavailability of dexmedetomidine after intranasal administration was good (65 %) but the interindividual variation was large (35-93 %). This observation attests to the need to develop an improved drug delivery system compared to the one used in the current study.

The volume, formulation and site of spray application may be of crucial importance when any drug is administered intranasally. Indeed, intranasal application failed in one subject, even though the use of the applicator had been practised. In real life, administration of an intranasal spray may be even more difficult to accomplish than in experimental settings, particularly in children. Therefore, development of an optimized formulation and nasal delivery system is obviously required for this route to be clinically applicable. However, it likely makes no great difference if part of the dexmedetomidine dose ends up in the pharynx and mouth, because dexmedetomidine is also readily absorbed from the oral mucosa (Anttila *et al.* 2003). Still, if the administered volume is too large, part of the drug may be swallowed, causing reduced bioavailability and diminished efficacy because of first-pass metabolism in the liver.

6.2 Dexmedetomidine pharmacokinetics in intensive care patients

6.2.1 Noncompartmental analysis

The pharmacokinetics of dexmedetomidine has mostly been studied in healthy subjects (Dyck *et al.* 1993b, Karol and Maze 2000, Anttila *et al.* 2003). There is one former study on the pharmacokinetics of dexmedetomidine during intensive care in postoperative coronary artery bypass patients, but the drug dose in that study was restrained to a maximum of 0.7 μg/kg/h and the mean duration of dexmedetomidine administration was only 10 h (range, 6 to 16 hours) (Venn *et al.* 2002). In the current study, the elimination half-life of dexmedetomidine after long infusions was comparable but still a little longer than reported previously for shorter dexmedetomidine infusions or in healthier patients or healthy volunteers (Karol and Maze 2000, Venn *et al.* 2002, Anttila *et al.* 2003). Nevertheless, the values for dexmedetomidine clearance and volume of distribution were in line with previous

reports. The slower elimination of dexmedetomidine as described by means of the elimination half-life may be attributable to the severe illness of our patients.

6.2.1.1 Variability of clearance at steady state

Clearance at steady state could be calculated in 116 cases during the dexmedetomidine infusions. The infusion rate was statistically significantly related to clearance at steady state in multivariate analysis, suggesting that dexmedetomidine exhibits non-linear pharmacokinetics. However, this is unlikely and contrasts with the aforementioned results. Instead, the increasing effect of infusion rate on dexmedetomidine clearance at steady state may be related to the patient's recovery: a severely ill patient with reduced hepatic blood flow likely requires only low doses of sedative agents, and when the patient is getting better with a simultaneous increase of hepatic blood flow and resulting improvement of dexmedetomidine clearance, he/she needs more sedatives, thus giving the erroneous impression of a relationship between dexmedetomidine clearance and the dose. Indeed, the calculated dexmedetomidine clearance was increased by 60% in a few days despite a constant infusion rate in the patient presented in Study V.

6.2.1.2 Linearity

The pharmacokinetics of dexmedetomidine appeared to be linear at least up to the dose of 2.5 μg/kg/h, as there was a strong linear relationship between the area under the dexmedetomidine concentration-time curve and the cumulative dexmedetomidine dose. This relationship means that when the dose of dexmedetomidine is increased, its plasma concentration increases in a linear fashion, with consequent potential pharmacological effects (Brocks and Mehvar 2010).

As dexmedetomidine decreases cardiac output and as hepatic blood flow primarily governs its elimination clearance (Dutta *et al.* 2000), it can be speculated whether the pharmacokinetics of dexmedetomidine at some point becomes non-linear, if the drug is administered in high enough doses. Indeed, dexmedetomidine concentrations (Figure 4) increased unexpectedly in one patient during the 24 hours prior to her death from 3.4 to 9.9 ng/ml with no signs of hepatic failure. She was afflicted with paralytic ileus and critical septic shock, and her cardiac index was only 0.4 to 1.3 l/min/m^2 during her last 24 hours. A post-mortem examination revealed that acute myocardial infarction with a ruptured myocardium and haemopericardium was the direct cause of her death. In the current case, it can be deduced that dexmedetomidine concentrations increased unexpectedly because of reduced hepatic blood flow. Thus, severely reduced liver blood flow, like in this case, may result in exceptionally high dexmedetomidine plasma concentrations.

6.2.2 Multicompartmental analysis

Dexmedetomidine concentrations in Study IV were described by a two-compartment model with significant covariate effects mainly affecting the elimination clearance and

the volume of distribution at steady state. Due to practical reasons, the last blood samples were obtained from the patients only a few hours after or occasionally even shortly prior to interrupting the dexmedetomidine infusion. This limitation may explain why a three-compartment model was not superior to the two-compartment model. However, dexmedetomidine pharmacokinetics could be adequately described by a two-compartment model in a previous study where the last sample was taken even 24 hours after discontinuation of the drug infusion (Venn *et al.* 2002). In that study, the authors reported a mean elimination clearance rate of 49.2 l/h, a distribution clearance rate of 135 l/h, a volume of distribution of 149 l and an elimination half-life of 3 h, which are similar to those observed in the current study. The values of the pharmacokinetic variables in the present study are quite close to the estimates reported previously in female surgical patients undergoing transphenoidal pituitary hypophysectomy (Talke *et al.* 1997). For the central volume of distribution, the mean value of 12.3 l observed in the current study is within the wide range from 8.0 l (Dyck *et al.* 1993a) up to 63.4 l (Lin *et al.* 2011) reported in previous studies. With the exception of one study (Dyck *et al.* 1993a), the context-sensitive half-times predicted by the models from different studies were fairly similar despite the wide range in certain parameters (Figure 10). The clearly longer context-sensitive half-time of the model of Dyck was for the most part caused by the small elimination clearance of 27.0 l/h. Nevertheless, the study design (length of post-infusion sampling time and time resolution of sampling) has a strong impact on the pharmacokinetic results. The context-sensitive half-time attained with a three-compartment model in Chinese patients (Lin *et al.* 2011) was almost identical to the current results.

6.2.3 Patient factors affecting dexmedetomidine pharmacokinetics

Previous population pharmacokinetic studies suggest that age, sex, body weight, lean body mass and body surface area do not affect dexmedetomidine pharmacokinetics. A small effect of height on dexmedetomidine clearance has been reported previously (Dyck *et al.* 1993a), but a clear increase of dexmedetomidine clearance with height was described in a recent study (Lin *et al.* 2011). The influence of height was described by a power model: $Cl = 0.47 \cdot (\text{height}/160\ \text{cm})^{6.42}$, meaning that dexmedetomidine clearance would increase by more than 100% as the height of a patient increases from 160 cm to 180 cm. Unfortunately, no standard error or confidence interval was provided for the large exponent, making it difficult to judge the reliability of the model. However, the large effect of height may partly be explained by ethnic differences, as the study of Lin was conducted in Chinese subjects.

Evaluation of the patient factors affecting the pharmacokinetics of dexmedetomidine was performed using two different approaches. In Study III, the relationship of baseline patient factors and noncompartmental pharmacokinetic parameters was analysed. These patient factors included gender, age, SAPS II score at screening, and heart rate, blood pressure, creatinine and creatinine clearance at baseline. In Study IV, a population pharmacokinetic approach was used, and age, sex, body mass, height, body mass index, lean body mass, cardiac output, plasma bilirubin and albumin

concentrations, PaO_2/FiO_2 (an oxygenation index), renal replacement therapy and renal function were used as covariates. In the noncompartmental analysis, the mean dexmedetomidine clearance was significantly higher and the mean elimination half-life significantly shorter in subjects with a baseline SAPS II score less than 42 as compared to subjects with baseline SAPS II scores > 42, and a linear correlation between dexmedetomidine clearance and baseline creatinine clearance was observed. In the population pharmacokinetic analysis, dexmedetomidine clearance decreased with decreasing cardiac output and with increasing age, whereas its volume of distribution at steady state was increased in patients with a low plasma albumin concentration. To summarize the results of the two different approaches, SAPS II score, creatinine clearance, cardiac output and age had an effect on dexmedetomidine clearance, SAPS II score had an effect on elimination half-life, and plasma albumin concentration had an effect on the volume of distribution at steady state.

As the SAPS II score is calculated by using, among other factors, information on the patient's chronic diseases, level of consciousness, age, systolic blood pressure, heart rate, temperature, PaO_2/FiO_2, urine output, serum urea, white blood cell count and plasma bilirubin level (Le Gall *et al.* 1993), it can be considered as an indicator of the general condition of the patient. Because of its unspecificity, it is difficult to evaluate its value and clinical significance. Additionally, all of the factors – or variables closely related to them – except plasma albumin concentration that were found to be associated with dexmedetomidine pharmacokinetics in the current studies are used in calculating the SAPS II score. Thus, it is not justified to conclude that the SAPS II score was an independent factor affecting the pharmacokinetics of dexmedetomidine.

In the population pharmacokinetic analysis, age and cardiac output were associated with dexmedetomidine clearance. An effect of cardiac output has been observed previously (Dutta *et al.* 2000), but association with age is a novel observation, even though at close inspection of the data of Venn (Venn *et al.* 2002), one may see dexmedetomidine clearance decreasing from 72.3 l/h in the youngest subject aged 35 years to 37.7 l/h in the oldest subject of 80 years, with a negative correlation ($r = -0.71$, $p = 0.02$) between age and clearance.

As renal function itself does not affect the pharmacokinetics of dexmedetomidine (De Wolf *et al.* 2001), it is hard to explain why creatinine clearance had an effect on the pharmacokinetics of dexmedetomidine in the traditional analysis. Interestingly, renal impairment, as assessed by the glomerular filtration rate, slightly affected dexmedetomidine clearance in the population pharmacokinetic analysis also. However, glomerular filtration rate was not included in the model, as drug clearance decreased with age and glomerular filtration rate was estimated by using a formula that includes age. Thus, one cannot clearly distinguish between the effect of age and the effect of renal impairment in this analysis. However, considering the results of the study by De Wolf (De Wolf *et al.* 2001), it is reasonable to think that renal function is related to the general condition of the patient, thus being a surrogate variable like the SAPS II score in this context.

In the population pharmacokinetic model, a low plasma albumin concentration increased the volume of distribution at steady state. As dexmedetomidine is rather highly (94%) bound to plasma proteins (Karol and Maze 2000) and a decreased albumin concentration may result in a higher proportion of unbound dexmedetomidine in blood, the drug's volume of distribution may consequently be increased. However, dexmedetomidine clearance was not associated with the plasma albumin concentration, which may be explained by dexmedetomidine being a high-extraction drug, the clearance of which is mainly determined by liver blood flow but less by protein binding (Dutta *et al.* 2000). Unfortunately, a low plasma albumin concentration may also be an indicator of the patient's poor general condition, like the SAPS II score.

The plasma bilirubin level was used as an indicator of hepatic function. Surprisingly, there was no relationship between dexmedetomidine clearance and the plasma bilirubin concentration, even though dexmedetomidine is mainly metabolized by the liver. The most likely explanation for this is that the plasma bilirubin concentration is an insensitive indicator of hepatic function. Additionally, for a high-extraction drug such as dexmedetomidine, hepatic clearance is for the most part determined by liver blood flow and less by intrinsic liver function. Furthermore, there were no patients with severely impaired hepatic function in the current series of studies.

6.2.4 Clinical relevance of the covariate effects

The clinical relevance of the covariate effects found in the population pharmacokinetic analysis was assessed by simulations. It was found that in elderly patients and in patients with hypoalbuminaemia, the terminal half-life and context-sensitive half-time of dexmedetomidine were increased, which may lead to prolonged sedation. The elimination clearance is the most important parameter for long-term drug dosing, as the infusion rate at steady state is determined by $I_{ss} = C_{target} \bullet Cl$, where C_{target} is the targeted plasma concentration. Dexmedetomidine clearance was about 25% smaller in an 80 year-old patient than in a 60 year-old patient. Therefore, the steady-state infusion rate for an elderly patient has to be reduced to gain equal dexmedetomidine plasma concentrations. Consequently, the possibility of potentially altered potency and duration of drug effects has to be taken into account when administering dexmedetomidine to elderly patients or to patients with significant hypoalbuminaemia.

6.2.5 Effect of renal replacement therapy

The possible effect of renal replacement therapy on the pharmacokinetics of dexmedetomidine has so far remained unknown. In the current study, four intensive care patients received renal replacement therapy with haemodialysis or haemodiafiltration, but there was no evidence that dexmedetomidine was extracted from plasma by these modes of renal replacement therapy. However, these sporadic observations do not justify any firm conclusions on this issue.

6.3 H-3 metabolite pharmacokinetics

The geometric mean value of the elimination half-life of the H-3 metabolite of dexmedetomidine was 9.1 h. This is clearly longer than that of the parent drug, and the geometric mean ratio of $AUC_{0-\infty}$ of the H-3 metabolite to that of dexmedetomidine was 1.47. Nevertheless, the affinity of the H-3 metabolite for α_2-adrenoceptors is less than 0.5 % that of dexmedetomidine (data on file, Orion Pharma) and therefore this phenomenon probably has no clinical implications. The ratio of $AUC_{0-\infty}$ of the H-3 metabolite to that of dexmedetomidine ranged from 0.29 to 4.4. This probably means that there is large interindividual variation in the activity of the different pathways of dexmedetomidine metabolism.

6.4 Pharmacological effects of dexmedetomidine

6.4.1 Sedative effect in healthy volunteers

Intranasally administered dexmedetomidine had similar sedative effects to those of intravenously administered dexmedetomidine, as assessed by the areas under the effect-time curves, but – as expected – the onset of the effect was delayed after intranasal dosing. The onset of the sedative effect of intranasally administered dexmedetomidine was at 30 - 45 min after administration, which is in concordance with the observed C_{max} of intranasal dexmedetomidine and preceding experience in paediatric patients (Yuen *et al.* 2010) and adult healthy volunteers (Yuen *et al.* 2007). If intranasally administered dexmedetomidine is used for premedication, it should optimally be administered 45-60 min before the start of the procedure.

6.4.2 Sedative effect in intensive care patients

In Study III, intensive care patients were given dexmedetomidine to attain a predefined level of sedation, mostly RASS 0 to -3. Significantly higher dexmedetomidine doses were given in the current study compared to those recommended in the summary information provided by the manufacturer at the time of the study. In eight of the 13 patients, the maximum rate of infusion was 2.5 μg/kg/h, and approximately 70% of the entire study duration was spent at the dose range of 1.4 – 2.5 μg/kg/h. Practically all patients received additional propofol (dose range 79-8505 mg/day) to achieve an adequate level of sedation. However, for two of the three patients receiving the highest doses of supplementary propofol, the RASS goal was changed to -4 for most of the study duration, denoting that they demanded deeper sedation because of their clinical state. The high propofol demand in these patients is in line with previous studies that have suggested that dexmedetomidine alone may not be sufficient in patients needing deep sedation (Ruokonen *et al.* 2009).

6.4.3 Haemodynamic effects in healthy volunteers

As expected, decreases in heart rate and blood pressure were observed after dexmedetomidine administration. The haemodynamic effects of intranasally administered dexmedetomidine were unexpectedly strong, as there were no differences between the administration routes in the haemodynamic outcome, except that a larger decrease was seen in heart rate after intravenous administration than after intranasal administration during the initial 0-30 min. Therefore, one has to be prepared for haemodynamic effects after intranasal administration, too.

6.4.4 Haemodynamic effects in intensive care patients

Bradycardia (Riker *et al.* 2009) and decreased blood pressure (Venn and Grounds 2001) have been reported in association with dexmedetomidine administration in intensive care patients. Additionally, transient hypertension has been reported primarily during the loading phase, likely due to high plasma dexmedetomidine concentrations and consequent vasoconstriction (Venn *et al.* 1999, Ebert *et al.* 2000). In the current study, the heart rate decreased after commencing the dexmedetomidine infusion, but no changes in average blood pressures were observed in this severely ill patient population. As one of the goals in intensive care is to keep haemodynamics stable by using different modalities of care, it can not be judged in this observational setting with no control phase whether the stability of the patients' haemodynamics was associated with the use of dexmedetomidine or with other interventions.

6.4.5 Sympatholytic effects in healthy volunteers

Plasma adrenaline and noradrenaline concentrations were measured to assess the sympatholytic effect of dexmedetomidine. The favourable sympatholytic effect of dexmedetomidine was achieved also after intranasal administration. As expected, there was a difference in plasma noradrenaline $AUC_{0–30\ min}$ between the intravenous and intranasal administration, reflecting slower onset of drug action after the latter.

6.4.6 Gastrointestinal effects in healthy volunteers

The administration of dexmedetomidine had significant inhibitory effects on gastric emptying and oro-caecal transit, as paracetamol t_{max} was increased to approximately four-fold, paracetamol $AUC_{0-90\ min}$ was decreased by 95% and oro-caecal transit time was increased to four-fold compared to placebo. This observation was consistent across all 12 subjects participating in the study.

It is considered desirable to commence enteral feeding at an early stage of intensive care unit stay, as early enteral feeding has been associated with reduced ICU and hospital mortality (Artinian *et al.* 2006). However, impaired gastrointestinal motility often prevents nasogastric feeding and increases the risk of aspiration. Traditionally, intensive care patients have been sedated with opioid-benzodiazepine combinations or with propofol. In previous studies, low-dose propofol has not inhibited gastric

emptying in healthy volunteers (Hammas *et al.* 1998, Chassard *et al.* 2002). This observation denotes that propofol should be rather safe in this respect, even if also propofol slightly lengthens oro-caecal transit time (Hammas *et al.* 1998). This notion is supported by a report that a combination of morphine and midazolam inhibited gastric emptying in critically ill patients compared to propofol (Nguyen *et al.* 2008).

It was somewhat surprising that dexmedetomidine had such a strong inhibitory effect on gastric emptying in the healthy volunteers of the present study, as this finding contrasts with previous results regarding the effects of another α_2-adrenoceptor agonist, clonidine (Asai *et al.* 1997b, Huilgol *et al.* 2002). This discrepancy might relate to dexmedetomidine being more selective than clonidine towards α_2-adrenoceptors (α_1: α_2 selectivity ratio 1:1600 for medetomidine vs 1:200 for clonidine) (Virtanen *et al.* 1988) or clonidine being a much weaker partial α_2-adrenoceptor agonist than dexmedetomidine (Peltonen *et al.* 1998), perhaps contributing to its lesser effect on gastric emptying. Interestingly, dexmedetomidine has been reported to have either small (Asai *et al.* 1997a) or no (Inada *et al.* 2004) effects on gastric emptying in rodents. This discrepancy between results concerning humans and rodents may result from dissimilarities in dosing or so far unknown inter-species variation in the effects of dexmedetomidine.

This result of the current study is clinically relevant, as the employed dose (0.7 μg/kg/h) is only half of the highest currently recommended dose (1.4 μg/kg/h) by the manufacturer for intensive care sedation (Orion Corporation 2011a). However, in a previous study, there was no difference in gastric emptying between intensive care patients sedated with dexmedetomidine or with propofol (Memis *et al.* 2006), indicating that the gastrointestinal effects of the two drugs are similar. As light propofol sedation does not inhibit gastric emptying in healthy volunteers (Hammas *et al.* 1998, Chassard *et al.* 2002), the results of Memis *et al.* suggest that dexmedetomidine should also not inhibit gastric emptying. This discrepancy between the results of the current study and those of Memis *et al.* may perhaps be explained by the smaller dexmedetomidine dose used by Memis and co-workers: they gave their patients dexmedetomidine only 0.2 μg/kg/h after a loading dose of 0.42 μg/kg, compared to the dose of 0.7 μg/kg/h after a loading dose of 1 μg/kg used in the current study. The inhibitory effect of dexmedetomidine on gastrointestinal motility is likely to be dose-dependent.

Morphine was chosen as a control drug to verify the reliability of the method because of its well-known inhibitory gastrointestinal effects. As it is known that a morphine dose of 0.05 mg/kg inhibits gastric emptying (Yuan *et al.* 1998) and gastrointestinal transit (Yuan *et al.* 1997) in healthy volunteers, it was decided to double the morphine dose to avoid a false negative result. Surprisingly, there were no statistically significant differences in the measured parameters between the placebo and morphine phases of the current study. The unexpectedly small gastrointestinal effects of morphine may have been caused by morphine being given as a 20-min infusion to avoid high peak plasma concentrations, which could have caused typical opioid adverse effects. Even if

there were no statistically significant differences between the placebo and morphine phases, it does not change the conclusion that dexmedetomidine had inhibitory gastrointestinal effects compared to placebo and morphine.

Gastric emptying and gastrointestinal transit were assessed in the same experimental session in order not to unnecessarily expose the healthy volunteers to a large number of drug administrations. Therefore, paracetamol and lactulose were administered simultaneously. However, lactulose has also been shown to slow gastric emptying (Miller *et al.* 1997), even though it is marketed as a laxative. It is possible that this property of lactulose may have masked the effect of morphine on gastric emptying compared to placebo, but a definitive explanation for why the gastrointestinal effects of morphine did not differ from those of placebo cannot be offered.

6.5 Safety of dexmedetomidine administration

6.5.1 Healthy volunteers

As expected, the employed moderate doses of dexmedetomidine did not cause haemodymic adverse events in healthy volunteers. More interestingly, the healthy volunteers reported no numbness, irritation, bleeding, bad taste or any other subjective effects after intranasally or intravenously administered dexmedetomidine. Additionally, no visual signs of local mucosal irritation, inflammation, bleeding or ulceration of the nasal mucosa were detected by the investigators. These findings suggest that the intranasal administration route might be an innocuous way to administer dexmedetomidine. However, one has to keep in mind the limited number of study subjects.

6.5.2 Intensive care patients

Four adverse events were regarded to be related to dexmedetomidine. These included three episodes of bradycardia and one incident of 1st degree atrioventricular block. Indeed, dexmedetomidine has been shown to have significant effects on cardiac conduction in paediatric patients, possibly related to a decrease of sympathetic tone in the central nervous system and/or a reflex response to the systemic vasoconstriction caused by dexmedetomidine (Hammer *et al.* 2008). However, these four adverse events all resolved after dose reduction and / or concomitant treatment.

Surprisingly, tachycardia was the most common adverse event with nine episodes detected after start of the dexmedetomidine treatment. Nevertheless, tachycardia is common in intensive care patients (Annane *et al.* 2008) and the definitions of tachycardia and bradycardia have an effect on their incidence. It is improbable that dexmedetomidine per se would induce tachycardia.

There were five episodes of hypotension and four episodes of hypertension. Both are acknowledged as side-effects of dexmedetomidine (Hospira Inc 2008), but their incidence depends on the employed definitions, as discussed above. Additionally, with regard to both hypotension and hypertension, as one of the goals in intensive care is to keep the patient's haemodynamics stable by using different modalities of care, the information value of this purely observational result is limited.

There are variable results on the effect of dexmedetomidine dose on the incidence of adverse events. According to some studies, higher doses of dexmedetomidine may more commonly result in hypotension or bradycardia, but there are also studies suggesting the opposite (Jones *et al.* 2011). In the current study, most of the adverse events during the dexmedetomidine treatment were detected at the highest dose level (1.4-2.5 μg/kg/h), but there was no clear relationship between the dexmedetomidine plasma concentration and the onset of the adverse events. However, it was not surprising that most of the adverse events occurred at the highest dose level, because most of the study duration was spent at this level. Additionally, most adverse events were considered to be related to the underlying critical illness, and none of the serious adverse events recorded in this study were considered to be related to dexmedetomidine, but were typical of severely ill patients.

6.6 Ethical considerations

The Ethics Committee of the Hospital District of Southwest Finland and the Finnish National Agency for Medicines approved all study protocols. The studies were conducted according to the revised Declaration of Helsinki of the World Medical Association and good clinical trial practice guidelines of the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. They were also registered in the ClinicalTrials.gov public registry.

The aims of the studies were considered to be scientifically justified and ethically acceptable, and the investigators were aware of the risks and ethical issues related with the study procedures. The investigators had no direct financial interests in dexmedetomidine or in the outcome of these studies.

Studies I and II were performed in healthy volunteers. All study subjects were appropriately informed of the discomforts and possible risks related to the studies and gave their voluntary informed consent after adequate time had elapsed since they received the information. Additional information was given if requested. The subjects were able to withdraw their consent at any time without loss of health care or other benefits. Additionally, no subject candidates belonging to vulnerable groups were included in these studies. The financial compensation received by the study subjects was in compliance with Finnish regulations and normal practice at the study site. Therefore, the financial compensation was not considered to represent undue enticement for participation. Taking all these facts into consideration, the recruitment in these studies can be regarded to have been performed in an acceptable way.

It was expected that the administered doses of dexmedetomidine and morphine would not significantly affect respiration and blood oxygen saturation. It was thought to be plausible that a marked decrease in heart rate and a small, temporary increase followed by a marked decrease in blood pressure would follow dexmedetomidine administration (Ebert *et al.* 2000). However, these effects were considered to be non-symptomatic in resting subjects. Thus, it was considered safe to participate in these studies.

In Study II, the subjects were given a single dose of morphine, a drug with potential for addiction. However, opioids including morphine are commonly used in hospitals for long periods and at larger doses without problems. Additionally, administration over 20 minutes reduced the possibility of adverse events and euphoric sensations, and the study subjects had filled an abuse questionnaire (Michna *et al.* 2004) in order to exclude persons susceptible to opioid addiction. Finally, a positive urine test result for drugs of abuse would have revealed persons already using opioids, benzodiazepines or other drugs of abuse. Hence, every effort was made to prevent harmful effects of opioid administration to the healthy volunteers.

At least one competent anaesthesiologist was present during the drug administrations and continuously monitored the safety of the study subjects. Possible adverse events would have been treated according to established acceptable medical practice, and study subjects were discharged only after they were fit for safe discharge. Under these conditions and other precautions, it was considered that the drug administrations did not constitute a health hazard for the subjects.

The study procedures included invasive procedures, namely cannulations of peripheral veins and an artery. All cannulations carry a small risk of bruising and thrombophlebitis. More serious complications are very rare (Scheer *et al.* 2002). A total blood volume of less than 300 ml was taken from each study subject during these studies. Hence, the risks involved in participating in Study I or II were not considered to cause a significant health hazard to the subjects.

Studies III and IV were performed in critically ill patients. In Study III, intensive care patients were considered eligible for the study, if they were prescribed light to moderate sedation and dexmedetomidine treatment was expected to be needed for at least 24 hours. In Study IV, the study subjects were recruited from an ICU patient population for whom the treating physician had prescribed dexmedetomidine infusion and it was probable that the length of dexmedetomidine treatment would be more than 48 hours.

Due to critical illness and need of sedation, it was not considered possible to obtain valid informed consent from the study subject candidates prior to participation in the study. Therefore, informed consent for the subject candidate to be included in the study was sought from the candidate's legal representative. They were provided with full and adequate verbal and written information regarding the objectives, procedures and possible risks and benefits of the study. The representatives' questions were answered and they were allowed sufficient time to make up their mind concerning the patient's

participation in the study. The representatives were also informed about the patient's right to withdraw from the study at any time without any penalty or loss of benefits to which the patient is otherwise entitled and about the possibility of audits and inspections of relevant parts of the patient's records by representatives of local or foreign competent authorities.

Dexmedetomidine administration was in line with the protocol used in everyday care in the ICU, and dexmedetomidine was started only to patients needing continuous sedation. Rescue treatment could be administered at any time in case of insufficient sedation, and the study treatment did not prevent any other modality of care. As the study subjects were already in the ICU due to their critical illness, no cannulations or other procedures were performed because of the study. Since dexmedetomidine does not appear to depress respiration, it was considered that participation does not delay weaning from assisted ventilation. Thus, participation in the studies was not regarded to be an additional risk for this high-risk patient population.

Side effects of dexmedetomidine include bradycardia, hypotension, hypertension and atrioventricular block. However, as they are likely to be concentration-dependent and usually respond to dose reduction, they were not considered as major risks in the ICU setting. Blood samples are drawn regularly from ICU patients, and participation in the study only insignificantly increased the amount of blood loss. Hence, it was considered that the possible adverse events and blood sampling did not constitute significant additional health hazards to the subjects.

6.7 Limitations of the studies

The range of the individual dexmedetomidine nasal bioavailability estimates was wide (35-93 %). This may be related to inaccuracies in intranasal administration of dexmedetomidine, since the absolute dose of intranasally administered dexmedetomidine remains uncertain even though administration had been practiced and the commercial application system used was specifically designed for nasal spray administration. No formal validation of the application system was performed, apart from verification of the dispensed volume by weighing. However, it is possible that the intranasally applied drug partly dripped from the nasal cavity into the pharynx and was swallowed, although the volume of the administered solution was small (0.1 ml per nostril) and the spraying was synchronized with the inspirium to maximize the spread of the aerosol within the nasal cavity.

The gastrointestinal effects of dexmedetomidine were studied in healthy volunteers. Therefore, the results cannot be directly extrapolated to critically ill intensive care patients. Surprisingly, there was only a tendency for impaired gastric emptying and gastrointestinal transit after morphine administration, but the differences compared to placebo were not statistically significant, challenging the validity of the study. In retrospect, the dose of morphine was obviously too small, although on the basis of

previous studies, the employed intravenous dose of morphine should have had prominent gastrointestinal effects (Yuan *et al.* 1997, Yuan *et al.* 1998). However, this deficiency does not change the conclusion that dexmedetomidine inhibited gastric emptying and gastrointestinal transit compared to placebo and morphine.

Many of the intensive care patients developed various circulatory problems during the study, which may have affected the pharmacokinetics of dexmedetomidine via possible reductions in hepatic blood flow.

In the population pharmacokinetic analysis, the short post-infusion sampling period did not allow the use of a three-compartment model, which may generally be better to characterize the pharmacokinetics of dexmedetomidine. Additionally, the covariates were partly inter-correlated and unspecific, so that one cannot say which physiological mechanisms relate to each of the covariate effects. Hence, the sum of these covariate effects may be regarded as a descriptor of the general condition of the patient. Although the median prediction error was reduced from -5.9% to -3.7% by including covariate effects, the remaining residual bias for the final population model suggests that some unexplained covariate effects may still have existed.

All intensive care patients received several concomitant medications during the studies. Even though none of the drugs administered are known to be potent inhibitors or inducers of the enzymes relevant for the pharmacokinetics of dexmedetomidine, it was impossible to systematically evaluate the possible effects of all concomitant treatments on the pharmacokinetics or pharmacodynamics of dexmedetomidine.

The small number of patients included in the studies further limits the generalization of the results, and one should not extrapolate the results beyond the ranges of the characteristics of the patients and the employed sedation regimens. Especially, the results cannot be extrapolated to patients with severe liver failure, because patients having severe hepatic impairment were not considered eligible for the studies.

6.8 Clinical aspects

As intranasally administered dexmedetomidine was efficacious and well tolerated, it may be rational to expand the scope of use of the drug and to study the clinical usefulness of intranasally administered dexmedetomidine for new indications such as premedication, maintenance of the day and night –cycle or management of refractory pain in palliative care.

Dexmedetomidine had significant inhibitory effects on gastric emptying and gastrointestinal transit in healthy volunteers. However, the clinical significance of this observation is not evident, as intensive care patients receive several concomitant treatments with different gastrointestinal effects. However, in case of clinically

significantly impaired gastrointestinal motility, it would be reasonable to consider discontinuing dexmedetomidine.

In critically ill patients, the elimination half-life of dexmedetomidine was comparable but somewhat longer than reported previously for infusions of shorter duration and in healthier patients or volunteers. Both old age and low plasma albumin levels caused prolongation of dexmedetomidine's elimination half-life and context-sensitive half-time. Furthermore, dexmedetomidine was well tolerated despite the employed high doses and prolonged administration. The clinical significance of the prolonged context-sensitive half-time is not obvious, as dexmedetomidine is dosed to effect and dexmedetomidine has few adverse effects that would e.g. lengthen time in the ventilator. Probably, the age and albumin levels of the patients have to be taken into consideration in extreme cases only. Thus, dexmedetomidine administration in high doses and prolonged infusions do not cause major concerns such as in case of benzodiazepines or propofol.

6.9 Future research needs

Intranasal administration of dexmedetomidine is a promising way to provide sedation and anxiolysis for certain patient groups like children and patients undergoing dental surgery (Yuen *et al.* 2008, Talon *et al.* 2009 Cheung *et al.* 2011). However, the interindividual variability in the drug's bioavailability was quite wide in the current study. Even though the therapeutic window of dexmedetomidine is rather broad (Ebert *et al.* 2000), it would be relevant to develop an optimized delivery system for the intranasal route to improve the bioavailability and reduce the interindividual variability.

Dexmedetomidine has been proposed to be used in the treatment of delirium at the end of life and terminal sedation (Prommer 2010), and in the management of refractory pain in palliative care settings (Coyne *et al.* 2010). Indeed, the intranasal route might be a feasible way to administer dexmedetomidine in these patients. Therefore, studies concerning intranasally administered dexmedetomidine in the above-mentioned indications are highly warranted.

Lack of enteral feeding has been shown to be associated with degeneration of gut structure and function in intensive care patients (Guglielmi *et al.* 2006), and early enteral feeding has been associated with reduced ICU and hospital mortality (Artinian *et al.* 2006). Therefore, enteral nutrition is often commenced at an early stage of the ICU stay. However, gastric emptying is often inadequate so that nasogastric feeding is not possible and the risk of aspiration of food is increased. Hence, it is important to find out factors causing untoward gastrointestinal effects. Even though dexmedetomidine showed detrimental effects on gastrointestinal function in the current study in healthy volunteers, it would be important to compare the effects of dexmedetomidine with those of alternatively used sedatives, such as propofol and

midazolam in healthy volunteers and real intensive care patients, as well as to study the effects of different drug combinations.

The SAPS II score, creatinine clearance, cardiac output, age and plasma albumin concentration were found to influence the pharmacokinetics of dexmedetomidine. Especially, the effects of age and plasma albumin levels should be evaluated in hypothesis-based studies to test their clinical relevance. Additionally, as the possible effects of renal replacement therapy on the pharmacokinetics of dexmedetomidine still remain unknown after the current study, further research designed specifically to assess this issue is warranted.

7 SUMMARY AND CONCLUSIONS

1. The average bioavailability of intranasally administered dexmedetomidine was good (65%), even if the interindividual variation was wide. Intranasally administered dexmedetomidine was efficacious and well tolerated, making it appropriate for clinical situations requiring light sedation. According to the current experimental results, intranasal dexmedetomidine should be applied 45-60 min prior to the desired moment of maximal effect.

2. Dexmedetomidine significantly inhibited gastric emptying and gastrointestinal transit in healthy volunteers, when compared to placebo and morphine.

3. The elimination half-life of dexmedetomidine after long-lasting infusions was comparable but somewhat longer than reported previously for infusions of shorter duration and in healthier patients or healthy volunteers. However, the estimates of clearance and volume of distribution were similar, even if an individual subject's clearance may vary during intensive care. Dexmedetomidine appears to have linear pharmacokinetics up to the studied dose rate of 2.5 μg/kg/h. Despite the employed high doses and the prolonged infusions, no new safety findings for dexmedetomidine were observed.

4. On average, the pharmacokinetic properties of dexmedetomidine in severely ill intensive care patients were similar to those found in previous studies of much shorter duration. Dexmedetomidine clearance was decreased in elderly patients, and the volume of distribution was increased in patients with low plasma albumin levels. Both old age and low plasma albumin caused prolongation of dexmedetomidine's elimination half-life and context-sensitive half-time. However, as dexmedetomidine is dosed to effect, it seems to be safe to administer it also as long-lasting, high-dose infusions.

8 ACKNOWLEDGEMENTS

The present series of studies was carried out at the Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Turku and Turku University Hospital, and the Department of Pharmacology, Drug Development and Therapeutics, University of Turku and TYKSLAB, Unit of Clinical Pharmacology, during the years 2007 – 2011. I am thankful to the heads of these departments, Professors Klaus Olkkola, Mika Scheinin and Risto Huupponen, for the opportunity to work in these excellent facilities.

The studies were financially supported by EVO grants 13821 and 13388 of the Hospital District of Southwest Finland, Turku, Finland, the Instrumentarium Research Foundation, Helsinki, Finland, and Orion Pharma, Espoo, Finland. These institutions are gratefully acknowledged.

Especially, I want to express my gratitude to the following persons:

Professor Klaus Olkkola for his friendly and skilled guidance. Despite his busy schedule, he has always had time for me, and the emails I have sent late in the evening have usually been answered by the next morning.

Docent Riku Aantaa for friendship and non-scientific emails in addition to the talented supervision. His wide knowledge of dexmedetomidine and positive attitude have been essential in carrying out these studies.

Docent Erkki Kentala for his skilful guidance in conducting clinical studies in intensive care unit and optimistic support in the never-ending process of patient recruitment. His role was crucial in initiating this series of studies.

Professor Mika Scheinin for his interest in my studies and help in preparing the manuscripts. I admire his wide knowledge of alpha$_2$-agonists and expertise in the English language. Furthermore, I appreciate his rapid response times.

Dr. Ruut Laitio and Dr. Sanna Vilo for practical help and companionship during these studies. Docent Tuula Manner for her human attitude and practical help. Dr. Maria Lahtinen and Dr. Juha-Pekka Kurvinen for their expertise in analyzing dexmedetomidine and H-3 metabolite concentrations. Dr. Maria Wendelin-Saarenhovi for sharing her expertise in evaluating gastric emptying and oro-caecal transfer. Professor Pertti J Neuvonen for providing paracetamol analyses. Mr. Andrew Wighton, Dr. Chris Garratt and Dr. Tuula Ahtola-Sätilä for co-authorship and providing me with background information on dexmedetomidine. Mr. Pasi Pohjanjousi for statistical

assistance. Dr. Harald Ihmsen, Professor Helmut Schwilden and Professor Jürgen Schüttler for population pharmacokinetic analysis.

The official reviewers of this thesis, Docent Anne Kuitunen and Docent Minna Tallgren, for their valuable comments and suggestions as well as their rapid response time.

Docent Juha Perttilä for his encouraging attitude and the opportunity to conduct the studies in the Intensive Care Unit 950. Mr. Keijo Leivo for skilful and reliable assistance during the studies in the intensive care unit. Ms. Elina Kahra and Ms. Laura Valve for expert assistance in sample preparation. Ms. Birgitta Kalvi and Ms. Anne Timonen for guidance in tacking through the reefs of ICH GCP Guidelines. Ms. Teija Lemmetyinen for invaluable help in running study days.

Ms. Aulikki Paakkunainen and Ms. Henna-Maija Ihander for secretarial assistance.

Colleagues at the Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine. Personnel of the Surgical Operating Ward 250. Personnel of the Intensive Care Unit 950 for invaluable help in collecting blood samples during night-time and positive attitude towards my studies. My new workmates at Emergency Medical Services.

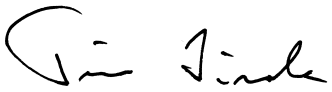
Riina and Ari-Pekka, Maria and Haade, Siru and Pate, Mari, Jyrki, Teppo and Stefan for friendship, good company and nice moments.

Guys of Saunaseura – Pasi, Markku, Kari and Timo – for true friendship but also for scientific and non-scientific discussions.

My parents Marjatta and Jouko Iirola for their support, love and help in managing everyday life of a family with children.

Finally, I want to thank my dear wife Karoliina and our children Pyry and Aura for their understanding, patience and love.

Turku, February 2012



9 REFERENCES

Aarons L. Population pharmacokinetics: theory and practice. Br J Clin Pharmacol 1991; 32:669-670

Abdalla MI, Al Mansouri F, Bener A. Dexmedetomidine during local anesthesia. J Anesth 2006; 20:54-56

Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948; 153:586-600

Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. Anesth Analg 1992; 75:932-939

Akada S, Takeda S, Yoshida Y, Nakazato K, Mori M, Hongo T, Tanaka K, Sakamoto A. The efficacy of dexmedetomidine in patients with noninvasive ventilation: a preliminary study. Anesth Analg 2008; 107:167-170

Al-Metwalli RR, Mowafi HA, Ismail SA, Siddiqui AK, Al-Ghamdi AM, Shafi MA, El-Saleh AR. Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. Br J Anaesth 2008; 101:395-399

Annane D, Sebille V, Duboc D, Le Heuzey JY, Sadoul N, Bouvier E, Bellissant E. Incidence and prognosis of sustained arrhythmias in critically ill patients. Am J Respir Crit Care Med 2008; 178:20-25

Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. Br J Clin Pharmacol 2003; 56:691-693

Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004; 98:153-158

Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006; 129:960-967

Asai T, Mapleson WW, Power I. Differential effects of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat. Br J Anaesth 1997a; 78:301-307

Asai T, Mapleson WW, Power I. Interactive effect of morphine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat. Br J Anaesth 1998; 80:63-67

Asai T, McBeth C, Stewart JI, Williams J, Vaughan RS, Power I. Effect of clonidine on gastric emptying of liquids. Br J Anaesth 1997b; 78:28-33

Aston-Jones G, Rajkowski J, Kubiak P, Alexinsky T. Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. J Neurosci 1994; 14:4467-4480

Ayoglu H, Altunkaya H, Ozer Y, Yapakci O, Ozkocak I, Oz O, Alpay A, Ugurbas SH. Dexmedetomidine sedation during cataract surgery under regional anaesthesia. Br J Anaesth 2007; 99:448

Barletta JF, Miedema SL, Wiseman D, Heiser JC, McAllen KJ. Impact of dexmedetomidine on analgesic requirements in patients after cardiac surgery in a fast-track recovery room setting. Pharmacotherapy 2009; 29:1427-1432

Bejian S, Valasek C, Nigro JJ, Cleveland DC, Willis BC. Prolonged use of dexmedetomidine in the paediatric cardiothoracic intensive care unit. Cardiol Young 2009; 19:98-104

Berkowitz DE, Price DT, Bello EA, Page SO, Schwinn DA. Localization of messenger RNA for three distinct alpha 2-adrenergic receptor subtypes in human tissues. Evidence for species heterogeneity and implications for human pharmacology. Anesthesiology 1994; 81:1235-1244

Biccard BM, Goga S, de Beurs J. Dexmedetomidine and cardiac protection for

non-cardiac surgery: a meta-analysis of randomised controlled trials. Anaesthesia 2008; 63:4-14

Billings FTt, Chen SW, Kim M, Park SW, Song JH, Wang S, Herman J, D'Agati V, Lee HT. Alpha2-adrenergic agonists protect against radiocontrast-induced nephropathy in mice. Am J Physiol Renal Physiol 2008; 295:F741-748

Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 1992; 77:1134-1142

Bockaert J, Pin JP. Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J 1999; 18:1723-1729

Bond A, Lader MH. The use of visual analogue scales in rating subjective feelings. Br J Med Psychol 1974; 1974:211-218

Brocks DR, Mehvar R. Rate and extent of drug accumulation after multiple dosing revisited. Clin Pharmacokinet 2010; 49:421-438

Brummett CM, Norat MA, Palmisano JM, Lydic R. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. Anesthesiology 2008; 109:502-511

Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. Anesthesiology 2009; 111:1111-1119

Bylund DB. Alpha-2 adrenoceptor subtypes: are more better? Br J Pharmacol 2005; 144:159-160

Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, Molinoff PB, Ruffolo RR, Jr., Trendelenburg U. International Union of Pharmacology nomenclature of adrenoceptors. Pharmacol Rev 1994; 46:121-136

Carroll CL, Krieger D, Campbell M, Fisher DG, Comeau LL, Zucker AR. Use of dexmedetomidine for sedation of children hospitalized in the intensive care unit. J Hosp Med 2008; 3:142-147

Chassard D, Lansiaux S, Duflo F, Mion F, Bleyzac N, Debon R, Allaouchiche B. Effects of subhypnotic doses of propofol on gastric emptying in volunteers. Anesthesiology 2002; 97:96-101

Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth 2011; 107:430-437

Choi HA, Ko SB, Presciutti M, Fernandez L, Carpenter AM, Lesch C, Gilmore E, Malhotra R, Mayer SA, Lee K, Claassen J, Schmidt JM, Badjatia N. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. Neurocrit Care 2011; 14:389-394

Chotani MA, Mitra S, Su BY, Flavahan S, Eid AH, Clark KR, Montague CR, Paris H, Handy DE, Flavahan NA. Regulation of alpha(2)-adrenoceptors in human vascular smooth muscle cells. Am J Physiol Heart Circ Physiol 2004; 286:H59-67

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41

Cooper L, Candiotti K, Gallagher C, Grenier E, Arheart KL, Barron ME. A randomized, controlled trial on dexmedetomidine for providing adequate sedation and hemodynamic control for awake, diagnostic transesophageal echocardiography. J Cardiothorac Vasc Anesth 2011; 25:233-237

Cortinez LI, Hsu YW, Sum-Ping ST, Young C, Keifer JC, Macleod D, Robertson KM, Wright DR, Moretti EW, Somma J. Dexmedetomidine pharmacodynamics: Part II: Crossover comparison of the analgesic effect of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004; 101:1077-1083

Coskuner I, Tekin M, Kati I, Yagmur C, Elcicek K. Effects of dexmedetomidine on the duration of anaesthesia and wakefulness in bupivacaine epidural block. Eur J Anaesthesiol 2007; 24:535-540

Coyne PJ, Wozencraft CP, Roberts SB, Bobb B, Smith TJ. Dexmedetomidine: exploring its potential role and dosing guideline for its use in

intractable pain in the palliative care setting. J Pain Palliat Care Pharmacother 2010; 24:384-386

De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001; 93:1205-1209

Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85:109-117

Devabhakthuni S, Pajoumand M, Williams C, Kufera JA, Watson K, Stein DM. Evaluation of Dexmedetomidine: Safety and Clinical Outcomes in Critically Ill Trauma Patients. J Trauma 2011; 71:1164-1171

Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. Crit Care Med 2010; 38:S231-243

Diaz SM, Rodarte A, Foley J, Capparelli EV. Pharmacokinetics of dexmedetomidine in postsurgical pediatric intensive care unit patients: preliminary study. Pediatr Crit Care Med 2007; 8:419-424

Drew GM, Whiting SB. Evidence for two distinct types of postsynaptic alpha-adrenoceptor in vascular smooth muscle in vivo. Br J Pharmacol 1979; 67:207-215

Drummond JC, Dao AV, Roth DM, Cheng CR, Atwater BI, Minokadeh A, Pasco LC, Patel PM. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. Anesthesiology 2008; 108:225-232

Drummond JC, Sturaitis MK. Brain tissue oxygenation during dexmedetomidine administration in surgical patients with neurovascular injuries. J Neurosurg Anesthesiol 2010; 22:336-341

Duffull SB, Wright DF, Winter HR. Interpreting population pharmacokinetic-pharmacodynamic analyses - a clinical viewpoint. Br J Clin Pharmacol 2011; 71:807-814

Dutta S, Lal R, Karol MD, Cohen T, Ebert T. Influence of cardiac output on dexmedetomidine pharmacokinetics. J Pharm Sci 2000; 89:519-527

Dyck JB, Maze M, Haack C, Azarnoff DL, Vuorilehto L, Shafer SL. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 1993a; 78:821-828

Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydro-chloride in adult human volunteers. Anesthesiology 1993b; 78:813-820

Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93:382-394

Eisenmann A, Amann A, Said M, Datta B, Ledochowski M. Implementation and interpretation of hydrogen breath tests. J Breath Res 2008; 2:046002

El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth 2009; 103:268-274

Elhakim M, Abdelhamid D, Abdelfattach H, Magdy H, Elsayed A, Elshafei M. Effect of epidural dexmedetomidine on intraoperative awareness and post-operative pain after one-lung ventilation. Acta Anaesthesiol Scand 2010; 54:703-709

Elvan EG, Oc B, Uzun S, Karabulut E, Coskun F, Aypar U. Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. Eur J Anaesthesiol 2008; 25:357-364

Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg 2010; 111:1548-1551

European Medicines Agency E, EU. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [Internet]. 1995 [cited 13.09.2011]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

European Medicines Agency E, EU. Assessment report Dexdor. 2011 [cited 18.11.2011]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002268/WC500115632.pdf

Fagerholm V, Gronroos T, Marjamaki P, Viljanen T, Scheinin M, Haaparanta M. Altered glucose homeostasis in alpha2A-adrenoceptor knockout mice. Eur J Pharmacol 2004; 505:243-252

Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol Pharmacol 2003; 63:1256-1272

Frumento RJ, Logginidou HG, Wahlander S, Wagener G, Playford HR, Sladen RN. Dexmedetomidine infusion is associated with enhanced renal function after thoracic surgery. J Clin Anesth 2006; 18:422-426

Fülöp K, Zádori Z, Rónai AZ, Gyires K. Characterisation of alpha2-adrenoceptor subtypes involved in gastric emptying, gastric motility and gastric mucosal defence. Eur J Pharmacol 2005; 528:150-157

Galitzky J, Larrouy D, Berlan M, Lafontan M. New tools for human fat cell alpha-2A adrenoceptor characterization. Identification on membranes and on intact cells using the new antagonist [3H]RX821002. J Pharmacol Exp Ther 1990a; 252:312-319

Galitzky J, Senard JM, Lafontan M, Stillings M, Montastruc JL, Berlan M. Identification of human platelet alpha 2-adrenoceptors with a new antagonist [3H]-RX821002, a 2-methoxy derivative of idazoxan. Br J Pharmacol 1990b; 100:862-866

Guglielmi FW, Boggio-Bertinet D, Federico A, Forte GB, Guglielmi A, Loguercio C, Mazzuoli S, Merli M, Palmo A, Panella C, Pironi L, Francavilla A. Total parenteral nutrition-related gastroenterological complications. Dig Liver Dis 2006; 38:623-642

Guinter JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. Am J Health Syst Pharm 2010; 67:1246-1253

Hammas B, Hvarfner A, Thorn SE, Wattwil M. Propofol sedation and gastric emptying in volunteers. Acta Anaesthesiol Scand 1998; 42:102-105

Hammer GB, Drover DR, Cao H, Jackson E, Williams GD, Ramamoorthy C, Van Hare GF, Niksch A, Dubin AM. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008; 106:79-83

Hannington-Kiff JG. Measurement of recovery from outpatient general anaesthesia with a simple ocular test. Br Med J 1970; 3:132-135

Heading RC, Nimmo J, Prescott LF, Tothill P. The dependence of paracetamol absorption on the rate of gastric emptying. Br J Pharmacol 1973; 47:415-421

Heeremans EH, Proost JH, Eleveld DJ, Absalom AR, Struys MM. Population pharmacokinetics and pharmacodynamics in anesthesia, intensive care and pain medicine. Curr Opin Anaesthesiol 2010; 23:479-484

Hieble JP. Subclassification and nomenclature of alpha- and beta-adrenoceptors. Curr Top Med Chem 2007; 7:129-134

Honey BL, Benefield RJ, Miller JL, Johnson PN. Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother 2009; 43:1506-1511

Hospira Inc. Precedex® [package insert]. Lake Forest (IL): Hospira Inc; 2008

Hsu YW, Cortinez LI, Robertson KM, Keifer JC, Sum-Ping ST, Moretti EW, Young CC, Wright DR, Macleod DB, Somma J. Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004; 101:1066-1076

Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76:334-341.

Hui YH, Marsh KC, Menacherry S. Analytical method development for the simultaneous quantitation of dexmedetomidine and three

potential metabolites in plasma. J Chromatogr A 1997; 762:281-291

Huilgol V, Evans J, Hellman RS, Soergel KH. Acute effect of clonidine on gastric emptying in patients with diabetic gastropathy and controls. Aliment Pharmacol Ther 2002; 16:945-950

Hunter JC, Fontana DJ, Hedley LR, Jasper JR, Lewis R, Link RE, Secchi R, Sutton J, Eglen RM. Assessment of the role of alpha2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. Br J Pharmacol 1997; 122:1339-1344

Inada T, Asai T, Yamada M, Shingu K. A new method using flow cytometry to measure the effects of drugs on gastric emptying and gastrointestinal transit in mice. Arzneimittelforschung 2004; 54:557-562

Jalonen J, Hynynen M, Kuitunen A, Heikkilä H, Perttilä J, Salmenperä M, Valtonen M, Aantaa R, Kallio A. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. Anesthesiology 1997; 86:331-345

Jansson CC, Pohjanoksa K, Lang J, Wurster S, Savola JM, Scheinin M. Alpha2-adrenoceptor agonists stimulate high-affinity GTPase activity in a receptor subtype-selective manner. Eur J Pharmacol 1999; 374:137-146

Jasper JR, Lesnick JD, Chang LK, Yamanishi SS, Chang TK, Hsu SA, Daunt DA, Bonhaus DW, Eglen RM. Ligand efficacy and potency at recombinant alpha2 adrenergic receptors: agonist-mediated [35S]GTPgammaS binding. Biochem Pharmacol 1998; 55:1035-1043

Jense RJ, Souter K, Davies J, Romig C, Panneerselvam A, Maronian N. Dexmedetomidine sedation for laryngeal framework surgery. Ann Otol Rhinol Laryngol 2008; 117:659-664

Ji QC, Zhou JY, Gonzales RJ, Gage EM, El-Shourbagy TA. Simultaneous quantitation of dexmedetomidine and glucuronide metabolites (G-Dex-1 and G-Dex-2) in human plasma utilizing liquid chromatography with tandem mass spectrometric detection. Rapid Commun Mass Spectrom 2004; 18:1753-1760

Jones GM, Murphy CV, Gerlach AT, Goodman EM, Pell LJ. High-dose dexmedetomidine for sedation in the intensive care unit: an evaluation of clinical efficacy and safety. Ann Pharmacother 2011; 45:740-747

Kallio A, Scheinin M, Koulu M, Ponkilainen R, Ruskoaho H, Viinamaki O, Scheinin H. Effects of dexmedetomidine, a selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. Clin Pharmacol Ther 1989; 46:33-42

Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand 2006; 50:222-227

Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha 2-adrenoceptor agonist effects by atipamezole in human volunteers. Br J Clin Pharmacol 1991; 31:160-165

Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990; 71:125-129

Karol MD, Maze M. Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. Baillière's Clinical Anaesthesiology 2000; 14:9

Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, Ozcan B. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth 2010; 57:39-45

Kivistö KT, Kallio A, Neuvonen PJ. Pharmacokinetics and pharmacodynamics of transdermal dexmedetomidine. Eur J Clin Pharmacol 1994; 46:345-349

Kohli U, Muszkat M, Sofowora GG, Harris PA, Friedman EA, Dupont WD, Scheinin M, Wood AJ, Stein CM, Kurnik D. Effects of variation in the human alpha2A- and alpha2C-adrenoceptor genes on cognitive tasks and pain perception. Eur J Pain 2010; 14:154-159

Konakci S, Adanir T, Yilmaz G, Rezanko T. The efficacy and neurotoxicity of dexmedetomidine

administered via the epidural route. Eur J Anaesthesiol 2008; 25:403-409

Kranke P, Eberhart LH, Roewer N, Tramer MR. Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. Anesth Analg 2002; 94:453-460

Kurnik D, Muszkat M, Li C, Sofowora GG, Friedman EA, Scheinin M, Wood AJ, Stein CM. Genetic variations in the alpha(2A)-adrenoreceptor are associated with blood pressure response to the agonist dexmedetomidine. Circ Cardiovasc Genet 2011; 4:179-187

Kurnik D, Muszkat M, Sofowora GG, Friedman EA, Dupont WD, Scheinin M, Wood AJ, Stein CM. Ethnic and genetic determinants of cardiovascular response to the selective alpha 2-adrenoceptor agonist dexmedetomidine. Hypertension 2008; 51:406-411

Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE. Substitution of a mutant alpha2a-adrenergic receptor via "hit and run" gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proceedings of the National Academy of Sciences of the United States of America 1997; 94:9950-9955

Langer SZ. Presynaptic regulation of the release of catecholamines. Pharmacol Rev 1980; 32:337-362

Laurila J. α2-adrenoceptors: Structure and ligand binding properties at the molecular level [Dissertation]. [Turku]: University of Turku; 2011. Table 3, Overview of physiological functions and pharmacological responses mediated by α2- adrenoceptor subtypes, as proposed from experiments with genetically engineered mice; p. 30.

Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-2963

Leino K, Hynynen M, Jalonen J, Salmenpera M, Scheinin H, Aantaa R. Renal effects of dexmedetomidine during coronary artery bypass surgery: a randomized placebo-controlled study. BMC Anesthesiol 2011; 11:9

Lin L, Guo X, Zhang MZ, Qu CJ, Sun Y, Bai J. Pharmacokinetics of dexmedetomidine in Chinese post-surgical intensive care unit patients. Acta Anaesthesiol Scand 2011; 55:359-367

Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, Fan SZ. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anaesth 2009; 102:117-122

Långsjö J, Kaskinoro K, Kaisti K, Aantaa R, Scheinin H. Dexmedetomidine and propofol have differential initial site of action. Euroanaesthesia 2010. Eur J Anaesthesiol 2010; 27:148

Ma D, Hossain M, Rajakumaraswamy N, Arshad M, Sanders RD, Franks NP, Maze M. Dexmedetomidine produces its neuroprotective effect via the alpha 2A-adrenoceptor subtype. Eur J Pharmacol 2004; 502:87-97

Mack PF, Perrine K, Kobylarz E, Schwartz TH, Lien CA. Dexmedetomidine and neurocognitive testing in awake craniotomy. J Neurosurg Anesthesiol 2004; 16:20-25

Martin E, Ramsay G, Mantz J, Sum-Ping ST. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. J Intensive Care Med 2003; 18:29-41

Mason KP, Zurakowski D, Zgleszewski S, Prescilla R, Fontaine PJ, Dinardo JA. Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric MRI. Paediatr Anaesth 2010; 20:516-523

Mason KP, Zurakowski D, Zgleszewski SE, Robson CD, Carrier M, Hickey PR, Dinardo JA. High dose dexmedetomidine as the sole sedative for pediatric MRI. Paediatr Anaesth 2008; 18:403-411

Maze M, Virtanen R, Daunt D, Banks SJ, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole sedative-anesthetic agent, on adrenal steroidogenesis: in vivo and in vitro studies. Anesth Analg 1991; 73:204-208

McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during

carotid endarterectomy performed under regional anesthesia. Anesth Analg 2006; 102:668-675

Memis D, Dokmeci D, Karamanlioglu B, Turan A, Ture M. A comparison of the effect on gastric emptying of propofol or dexmedetomidine in critically ill patients: preliminary study. Eur J Anaesthesiol 2006; 23:700-704

Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004; 98:835-840

Michna E, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, Palombi D, Jamison RN. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. J Pain Symptom Manage 2004; 28:250-258

Miller MA, Parkman HP, Urbain JL, Brown KL, Donahue DJ, Knight LC, Maurer AH, Fisher RS. Comparison of scintigraphy and lactulose breath hydrogen test for assessment of orocecal transit: lactulose accelerates small bowel transit. Dig Dis Sci 1997; 42:10-18

Muthig V, Gilsbach R, Haubold M, Philipp M, Ivacevic T, Gessler M, Hein L. Upregulation of soluble vascular endothelial growth factor receptor 1 contributes to angiogenesis defects in the placenta of alpha 2B-adrenoceptor deficient mice. Circ Res 2007; 101:682-691

Muzi M, Goff DR, Kampine JP, Roerig DL, Ebert TJ. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology 1992; 77:864-871

Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003; 98:428-436

Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C, Ching K, Bellon M, Holloway RH. The effects of sedation on gastric emptying and intra-gastric meal distribution in critical illness. Intensive Care Med 2008; 34:454-460

Nicholas AP, Pieribone V, Hokfelt T. Distributions of mRNAs for alpha-2 adrenergic receptor subtypes in rat brain: an in situ hybridization study. J Comp Neurol 1993; 328:575-594

O'Connor M, Bucknall T, Manias E. Sedation management in Australian and New Zealand intensive care units: doctors' and nurses' practices and opinions. Am J Crit Care 2010; 19:285-295

Orion Corporation. Dexdor® [summary of product characteristics]. Espoo, Finland: Orion Corporation; 2011a

Orion Corporation. Orion Corporation Stock exchange releases September 21st 2011. Espoo, Finland: Orion Corporation; 2011b

Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007; 298:2644-2653

Peltonen JM, Pihlavisto M, Scheinin M. Subtype-specific stimulation of [35S]GTPgammaS binding by recombinant alpha2-adrenoceptors. Eur J Pharmacol 1998; 355:275-279

Perälä M, Hirvonen H, Kalimo H, Ala-Uotila S, Regan JW, Akerman KE, Scheinin M. Differential expression of two alpha 2-adrenergic receptor subtype mRNAs in human tissues. Brain Res Mol Brain Res 1992; 16:57-63

Peterhoff M, Sieg A, Brede M, Chao CM, Hein L, Ullrich S. Inhibition of insulin secretion via distinct signaling pathways in alpha2-adrenoceptor knockout mice. Eur J Endocrinol 2003; 149:343-350

Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M, Lerman J. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology 2006; 105:1098-1110

Phillips JK, Vidovic M, Hill CE. Variation in mRNA expression of alpha-adrenergic, neurokinin and muscarinic receptors amongst four arteries of the rat. J Auton Nerv Syst 1997; 62:85-93

Potts AL, Anderson BJ, Warman GR, Lerman J, Diaz SM, Vilo S. Dexmedetomidine pharmacokinetics in pediatric intensive care--a pooled analysis. Paediatr Anaesth 2009; 19:1119-1129

Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. Paediatr Anaesth 2008; 18:722-730

Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, James RL, Bennett J, Butterworth J. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg 2002; 95:1052-1059

Prommer E. Dexmedetomidine: Does it Have Potential in Palliative Medicine? Am J Hosp Palliat Care 2010;

Pufal E, Sykutera M, Rochholz G, Schutz HW, Sliwka K, Kaatsch HJ. Determination of paracetamol (acetaminophen) in different body fluids and organ samples after solid-phase extraction using HPLC and an immunological method. Fresenius J Anal Chem 2000; 367:596-599

Read NW, Al-Janabi MN, Bates TE, Holgate AM, Cann PA, Kinsman RI, McFarlane A, Brown C. Interpretation of the breath hydrogen profile obtained after ingesting a solid meal containing unabsorbable carbohydrate. Gut 1985; 26:834-842

Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009; 301:489-499

Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and applications, 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2011

Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, Sarapohja T, Bratty JR, Takala J. Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation. Intensive Care Med 2009; 35:282-290

Rutkowska K, Knapik P, Misiolek H. The effect of dexmedetomidine sedation on brachial plexus block in patients with end-stage renal disease. Eur J Anaesthesiol 2009; 26:851-855

Sakurai Y, Obata T, Odaka A, Terui K, Tamura M, Miyao H. Buccal administration of dexmedetomidine as a preanesthetic in children. J Anesth 2010; 24:49-53

Salonen JS. Tissue-specificity of hydroxylation and N-methylation of arylalkylimidazoles. Pharmacol Toxicol 1991; 69:1-4

Salonen JS, Eloranta M. Biotransformation of medetomidine in the rat. Xenobiotica 1990; 20:471-480

Scheer B, Perel A, Pfeiffer UJ. Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. Crit Care 2002; 6:199-204

Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and peroperative fentanyl. Br J Anaesth 1992a; 68:126-131

Scheinin H, Karhuvaara S, Olkkola KT, Kallio A, Anttila M, Vuorilehto L, Scheinin M. Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. Clin Pharmacol Ther 1992b; 52:537-546

Scheinin M, Karhuvaara S, Ojala-Karlsson P, Kallio A, Koulu M. Plasma 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are insensitive indicators of alpha 2-adrenoceptor mediated regulation of norepinephrine release in healthy human volunteers. Life Sci 1991; 49:75-84

Scheinin M, Lomasney JW, Hayden-Hixson DM, Schambra UB, Caron MG, Lefkowitz RJ, Fremeau RT, Jr. Distribution of alpha 2-adrenergic receptor subtype gene expression in rat brain. Brain Res Mol Brain Res 1994; 21:133-149

Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care

unit patients. Am J Respir Crit Care Med 2002; 166:1338-1344

Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 1994; 10:392-404

Snapir A, Posti J, Kentala E, Koskenvuo J, Sundell J, Tuunanen H, Hakala K, Scheinin H, Knuuti J, Scheinin M. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. Anesthesiology 2006; 105:902-910

Stern TA, Gross AF, Stern TW, Nejad SH, Maldonado JR. Current approaches to the recognition and treatment of alcohol withdrawal and delirium tremens: "old wine in new bottles" or "new wine in old bottles". Prim Care Companion J Clin Psychiatry 2010; 12:

Stone LS, MacMillan LB, Kitto KF, Limbird LE, Wilcox GL. The alpha2a adrenergic receptor subtype mediates spinal analgesia evoked by alpha2 agonists and is necessary for spinal adrenergic-opioid synergy. J Neurosci 1997; 17:7157-7165

Su F, Hammer GB. Dexmedetomidine: pediatric pharmacology, clinical uses and safety. Expert Opin Drug Saf 2011; 10:55-66

Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. Anesth Analg 1997; 85:1136-1142

Talon MD, Woodson LC, Sherwood ER, Aarsland A, McRae L, Benham T. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. J Burn Care Res 2009; 30:599-605

Toader E, Cividjian A, Quintin L. Recruitment of cardiac parasympathetic activity: effects of clonidine on cardiac vagal motoneurones, pressure lability, and cardiac baroreflex slope in rats. Br J Anaesth 2009; 102:322-330

Trendelenburg AU, Sutej I, Wahl CA, Molderings GJ, Rump LC, Starke K. A re-investigation of questionable subclassifications of presynaptic alpha2-autoreceptors: rat vena cava, rat atria, human kidney and guinea-pig urethra. Naunyn Schmiedebergs Arch Pharmacol 1997; 356:721-737

Tsai CJ, Chu KS, Chen TI, Lu DV, Wang HM, Lu IC. A comparison of the effectiveness of dexmedetomidine versus propofol target-controlled infusion for sedation during fibreoptic nasotracheal intubation. Anaesthesia 2010; 65:254-259

Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shah M, Provost DA. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg 2008; 106:1741-1748

U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry. Population pharmacokinetics. U.S. Department of Health and Human Services, Food and Drug Administration; 1999

U.S. Department of Health and Human Services. Food and Drug Administration. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [cited 13.09.2011]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

Usta B, Gozdemir M, Demircioglu RI, Muslu B, Sert H, Yaldiz A. Dexmedetomidine for the prevention of shivering during spinal anesthesia. Clinics (Sao Paulo) 2011; 66:1187-1191

Ustun Y, Gunduz M, Erdogan O, Benlidayi ME. Dexmedetomidine versus midazolam in outpatient third molar surgery. J Oral Maxillofac Surg 2006; 64:1353-1358

Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, Vedio A, Singer M, Feneck R, Treacher D, Willatts SM, Grounds RM. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999; 54:1136-1142

Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth 2001; 86:650-656

Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth 2001; 87:684-690

Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care 2000; 4:302-308

Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth 2002; 88:669-675

Villela NR, do Nascimento Junior P, de Carvalho LR, Teixeira A. Effects of dexmedetomidine on renal system and on vasopressin plasma levels. Experimental study in dogs. Rev Bras Anestesiol 2005; 55:429-440

Vilo S, Rautiainen P, Kaisti K, Aantaa R, Scheinin M, Manner T, Olkkola KT. Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. Br J Anaesth 2008; 100:697-700

Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol 1988; 150:9-14

Wijeysundera DN, Bender JS, Beattie WS. Alpha-2 adrenergic agonists for the prevention of cardiac complications among patients undergoing surgery. Cochrane Database Syst Rev 2009; CD004126

Wright PM. Population based pharmacokinetic analysis: why do we need it; what is it; and what has it told us about anaesthetics? Br J Anaesth 1998; 80:488-501

Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med 2009; 37:3031-3039

Yuan CS, Foss JF, O'Connor M, Roizen MF, Moss J. Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol 1998; 38:1017-1020

Yuan CS, Foss JF, Osinski J, Toledano A, Roizen MF, Moss J. The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time. Clin Pharmacol Ther 1997; 61:467-475

Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL, Yuen MK. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesthesia 2010;

Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg 2008; 106:1715-1721

Yuen VM, Irwin MG, Hui TW, Yuen MK, Lee LH. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg 2007; 105:374-380

Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 1990; 70:624-630

Zub D, Berkenbosch JW, Tobias JD. Preliminary experience with oral dexmedetomidine for procedural and anesthetic premedication. Paediatr Anaesth 2005; 15:932-938