Clin Pharmacokinet (2017) 56:893–913
DOI 10.1007/s40262-017-0507-7

REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine

Maud A. S. Weerink[1] · Michel M. R. F. Struys[1,2] · Laura N. Hannivoort[1] · Clemens R. M. Barends[1] · Anthony R. Absalom[1] · Pieter Colin[1,3]

Published online: 19 January 2017

Abstract Dexmedetomidine is an α_2-adrenoceptor agonist with sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, and minimal depression of respiratory function. It is potent and highly selective for α_2-receptors with an α_2:α_1 ratio of 1620:1. Hemodynamic effects, which include transient hypertension, bradycardia, and hypotension, result from the drug's peripheral vasoconstrictive and sympatholytic properties. Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic α_2-receptors in the locus coeruleus, thereby inducting a state of unconsciousness similar to natural sleep, with the unique aspect that patients remain easily rousable and cooperative. Dexmedetomidine is rapidly distributed and is mainly hepatically metabolized into inactive metabolites by glucuronidation and hydroxylation. A high inter-individual variability in dexmedetomidine pharmacokinetics has been described, especially in the intensive care unit population. In recent years, multiple pharmacokinetic non-compartmental analyses as well as population pharmacokinetic studies have been performed. Body size, hepatic impairment, and presumably plasma albumin and cardiac output have a significant impact on dexmedetomidine pharmacokinetics. Results regarding other covariates remain inconclusive and warrant further research. Although initially approved for intravenous use for up to 24 h in the adult intensive care unit population only, applications of dexmedetomidine in clinical practice have been widened over the past few years. Procedural sedation with dexmedetomidine was additionally approved by the US Food and Drug Administration in 2003 and dexmedetomidine has appeared useful in multiple off-label applications such as pediatric sedation, intranasal or buccal administration, and use as an adjuvant to local analgesia techniques.

✉ Michel M. R. F. Struys
m.m.r.f.struys@umcg.nl

[1] Department of Anesthesiology, University of Groningen, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands

[2] Department of Anesthesia and Peri-operative Medicine, Ghent University, Ghent, Belgium

[3] Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium

Key Points

Pharmacokinetic studies have shown that body size and hepatic function have a significant influence on the pharmacokinetic profile of dexmedetomidine. Plasma albumin and cardiac output are suggested to have an impact on the apparent volume of distribution and clearance. Studies of the influence of other patient characteristics have produced inconclusive results.

Unlike sedative drugs such as propofol and the benzodiazepines, dexmedetomidine does not act at the gamma-aminobutyric acid (GABA) receptors. It induces sedation through activation of α_2-receptors in the locus coeruleus and induces a state mimicking natural sleep. Whilst sedated, respiration is minimally affected and patients remain rousable. Side effects are mainly hemodynamic and include hypertension, hypotension, and bradycardia as a result of vasoconstriction, sympatholysis, and baroreflex-mediated parasympathetic activation.

Further research is needed to investigate the clinical feasibility of different promising off-label indications, such as use in the pediatric and geriatric population, intranasal dexmedetomidine administration, its use as an adjuvant to prolong peripheral or spinal nerve blocks, and the potential of dexmedetomidine to reduce opioid consumption.

1 Introduction

Dexmedetomidine is a selective and potent α_2-adrenoceptor agonist that is used for its anxiolytic, sedative, and analgesic properties [1]. It has been registered in USA since 1999 (Precedex®; Hospira, Lake Forrest, IL, USA). Originally, it was only approved for intravenous (IV) administration for sedation of mechanically ventilated adult patients in the intensive care unit (ICU), for up to 24 h [2]. In 2008, an additional indication was granted in USA, which allowed the use of dexmedetomidine for the sedation of non-intubated patients prior to and/or during surgical and other procedures. Since 2011, dexmedetomidine has been approved in the European Union for the sedation of adult ICU patients requiring a sedation level at which patients remain rousable in response to verbal stimulation (Dexdor®; Orion Corporation, Espoo, Finland) [3]. On a more global perspective, differences in approved indications of dexmedetomidine exist. In addition to this, off-label use is frequently reported in the literature.

Compared with clonidine, an α_2-agonist that has been used for several decades, dexmedetomidine has a greater selectivity for α_2-receptors (α_2:α_1 ratio of 1620:1 vs. 220:1) [4]. As central α_1-adrenoceptor activation counteracts the sedative α_2 effects, dexmedetomidine is a more potent sedative than clonidine [5]. An important feature of dexmedetomidine-based sedation is that patients remain easily rousable [6]. This aspect, combined with the minimal influence on respiration, makes dexmedetomidine an interesting alternative sedative in many procedures, such as awake craniotomies and conscious sedation [7].

Side effects of dexmedetomidine are mainly restricted to hemodynamic alterations. These include hypertension, bradycardia, and hypotension owing to pre- and postsynaptic α_2-receptor activation, which causes vasoconstriction, vasodilatation, and reflex bradycardia [8, 9]. Moreover, dexmedetomidine has been shown to attenuate stress responses, thereby creating a more stable hemodynamic profile during stressful events such as surgery or anesthetic induction [10–12]. The aim of this article is to critically review and summarize published data on the clinical pharmacokinetics and pharmacodynamics of dexmedetomidine in healthy volunteers, the targeted patient populations, and several special patient populations. This review also critically addresses several new clinical applications of dexmedetomidine that have surfaced more recently.

2 Methods

The MEDLINE database was searched through PubMed. All English articles with a title containing dexmedetomidine and an abstract or title containing 'pharmacokinetic(s)', 'pharmacodynamics(s)' and/or 'pharmacology' were saved in a Mendeley library [13]. Additional searches were performed including the keywords 'hepatic failure', 'renal failure', 'elderly', 'pediatric', 'neonate(s)', 'interactions', 'obese', 'analgesia', and 'intranasal'. After screening titles for possible relevance, papers were added to the Mendeley Library. All abstracts were screened and when considered relevant, the paper's full text was obtained. Bibliographies of articles were reviewed and as such additional potentially relevant papers were identified and added to the library.

3 Drug Formulations and Dosing Regimens

Dexmedetomidine, or 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, with molecular formula $C_{13}H_{16}N_2$ [14], is the dextro-enantiomer of medetomidine, which is used as a

sedative and analgesic in veterinary medicine. Dexmedetomidine is commercially available as a water-soluble HCl salt. Vials of Dexdor® and Precedex® contain a concentrate of dexmedetomidine hydrochloride, equivalent to 100 μg/mL dexmedetomidine. Prior to infusion, this is diluted to 4 or 8 μg/mL. Precedex is also available in pre-diluted solutions containing the required concentrations of 4 μg/mL in sodium chloride 0.9% [2, 3]. The Dexdor summary of product characteristics advises an initial infusion rate of 0.7 μg/kg/h without a loading dose, followed by titration to the desired effect using a dose range of 0.2–1.4 μg/kg/h [3]. The Precedex label specifies a dosing regimen consisting of a 1-μg/kg loading dose in 10 min followed by a maintenance infusion of 0.2–0.7 μg/kg/h for ICU sedation. For procedural sedation, a loading dose of 1 μg/kg in 10 min followed by a maintenance infusion of 0.6 μg/kg/h, titrated to the desired clinical effect with doses ranging from 0.2 to 1 μg/kg/h, is recommended. Alternative dosing regimens can be considered in frail or elderly patients [2].

4 Pharmacokinetics

4.1 Absorption

Although dexmedetomidine is only registered for IV use, multiple routes of administration have been investigated. With extravascular administration, one can avoid the high peak plasma levels normally seen after IV administration. After oral administration, an extensive first-pass effect is observed, with a bioavailability of 16% [15]. Dexmedetomidine is well absorbed through the intranasal and buccal mucosae, a feature that could be of benefit when using dexmedetomidine in uncooperative children or geriatric patients (Sect. 9) [15–18].

4.2 Distribution

Dexmedetomidine is a highly protein-bound drug. In plasma, 94% of dexmedetomidine is bound to albumin and α_1-glycoprotein. Pre-marketing studies with radioactively labeled dexmedetomidine, showed a rapid and wide distribution throughout the body. In pre-clinical animal studies, it was found that dexmedetomidine readily crosses the blood–brain and placenta barriers [2, 3]. Using non-compartmental analysis, a distribution half-life of about 6 min was found in healthy volunteers [15, 19]. The apparent volume of distribution was found to be related to body weight, with a volume of distribution at steady state in healthy volunteers of approximately 1.31–2.46 L/kg (90–194 L) [16, 19–21]. In ICU patients, values are highly variable and mean volumes of distribution from 109 to 223 L have been reported [22–24]. After long-term infusion in ICU patients with hypoalbuminemia, an increased volume of distribution at steady state was observed [23–25].

4.3 Metabolism and Elimination

Dexmedetomidine is eliminated mainly through biotransformation by the liver. A hepatic extraction ratio of 0.7 was found [26]. Less than 1% is excreted unchanged with metabolites being excreted renally (95%) and fecally (4%) [2, 3, 19]. Direct N-glucuronidation by uridine 5′-diphospho-glucuronosyltransferase (UGT2B10, UGT1A4) accounts for about 34% of dexmedetomidine metabolism. In addition, hydroxylation mediated by cytochrome P450 (CYP) enzymes (mainly CYP2A6) was demonstrated in human liver microsomes [19, 27, 28]. In a pre-marketing ADME study by Abbott Laboratories, a single injection of 2 μg/kg radioactively labeled dexmedetomidine was given to healthy volunteers. The majority of the total plasma radioactivity area under the curve consisted of dexmedetomidine (14.7%), the N-glucuronide isomers G-dex-1 (35%) and G-dex2 (6%), the O-glucuronide of hydroxylated N-methyl dexmedetomidine (H-1) (21%), and the imidazole oxidation product H-3 (10%) [19, 28]. These metabolites were 100-fold less potent in the α_2-receptor assay and therefore considered inactive. No relevant chiral inversion to the inactive levo-enantiomer was found [28].

An elimination half-life of 2.1–3.1 h is reported in healthy volunteers [15, 16, 19, 20, 29, 30]. In ICU patients, similar values were found, with half-lives ranging from 2.2 to 3.7 h [22, 23, 25]. Non-compartmental analysis showed that dexmedetomidine clearance in healthy adult volunteers is approximately 0.6–0.7 L/min. Values range from 0.51 to 0.89 L/min [15, 19–21, 29, 30], with the highest value of 0.89 L/min being found by Wolf et al. in volunteers with a relatively high body weight (mean 93.5 kg) [20]. In ICU patients, (mostly post-surgical) clearance is similar to the clearance found in healthy volunteers and ranges from 0.53 to 0.80 [22, 23, 25].

For dexmedetomidine, prolonged [23, 24] as well as shortened [25] elimination half-lives have been reported for patients with hypoalbuminemia. Clearance however, is only marginally affected by hypoalbuminemia [23, 25]. This is in line with the "well-stirred" liver model, which states that for compounds with a high extraction ratio, liver blood flow is the most important factor governing hepatic clearance and changes in plasma protein levels are expected not to result in increased drug clearance [31]. The impact on dexmedetomidine clearance as a result of changes in liver blood flow, via changes in cardiac output, was studied by Dutta et al. [26]. They describe an estimated reduction in cardiac output of 19% associated with a

reduced clearance of 12% at plasma dexmedetomidine levels of 1.2 ng/mL (see also Sect. 5).

4.4 Dose Proportionality and Inter-Individual Variability

Within the therapeutic range, dose proportionality has been shown for dexmedetomidine [2, 3]. No relevant time dependency has been reported. Nevertheless, a high inter-individual variability is observed for clearance and distribution volumes. Hypoalbuminemia, end-organ damage, changes in hemodynamics, and decreased cardiac output may all contribute to a high inter-individual variability, especially in the ICU population [2, 3, 23, 24, 32].

Drug pharmacokinetics might be affected by ethnicity, especially when a drug is highly protein bound or undergoes hepatic metabolism [33]. A few small studies evaluated the role of race in dexmedetomidine pharmacokinetics/pharmacodynamics, but no clinically relevant influence was observed [34, 35]. Furthermore, Kohli et al. genotyped 40 subjects for five common CYP2A6 alleles and grouped them into normal ($n = 33$), intermediate ($n = 5$), and slow ($n = 2$) metabolizers. Although their study population was small and effects could have been obscured by the complex clinical situation, they found no significant influence of these genotypes on dexmedetomidine disposition in ICU patients [36]. Multiple other studies have evaluated the role of α-2A, -2B, and -2C adrenoceptor polymorphisms, but no recommendations to guide clinical dosing regimens have yet been derived [37].

5 Population Pharmacokinetic Modeling

5.1 Adult Population

Several population pharmacokinetic (PopPK) models have been developed to describe the pharmacokinetics of IV administered dexmedetomidine in the adult population. For a complete overview, the reader is redirected to Table 1. Most of these models were derived from a small group of postoperative ICU patients (median sample size 21, range 8–40) [22, 32, 38–41] or healthy volunteers (median sample size 17, range 10–24) [21, 26, 29, 42]. In addition, Välitalo et al. [24] developed a PopPK model from three phase III trials in which a prolonged dexmedetomidine dosing regimen was evaluated in critically ill patients (sample size 527).

Target-controlled infusion (TCI) was used in several studies to target a specific, predicted dexmedetomidine plasma concentration [38] or a sequence of plasma concentrations according to a "step-up" dosing design [21, 26, 42]. Dexmedetomidine plasma targets ranged from 0.49 to 8 ng/mL. In the other studies, dexmedetomidine was delivered via a combination of a short (5–10 min) loading dose followed by a maintenance dose. Loading doses were administered at infusion rates ranging from 0.5 to 6 μg/kg/h and maintenance infusion rates ranged from 0.1 to 2.5 μg/kg/h, and were maintained for between 50 min and 96 h. In contrast to these fixed dosing designs, in the study by Välitalo et al., the maintenance dose was individualized to achieve a Richmond Agitation-Sedation Scale between 0 and −3, resulting in maintenance dose levels varying between 0.2 and 1.4 μg/kg/h.

In most studies, a two-compartment PK model with zero-order input to and linear elimination from the central compartment was used to describe dexmedetomidine disposition and elimination. Four investigators [21, 26, 39, 42] found that a three-compartment PK model best described dexmedetomidine PK and the analysis by Välitalo et al. reported a one-compartment PK model as their final PK model. To describe the observed variability in dexmedetomidine pharmacokinetics across and within subjects, different covariate models have been suggested. The central and/or peripheral volumes of distribution (V_1, V_2, V_3) were found to correlate with a subject's age [29, 41], body weight [41, 42], fat free mass [40], serum albumin level [24, 32] and/or whether or not a subject was undergoing surgery [40]. The elimination and/or distributional clearance (CL, Q_2, Q_3) was found to vary significantly according to height [21, 39], body weight [24, 42], or fat (free) mass [40], age [32], cardiac output [26, 32], plasma albumin level [29] and/or alanine aminotransferase activity [41].

In Fig. 1, the impact of the different covariate models on the plasma concentration time profile is shown. For this, a 35-μg loading dose infused over 10 min (i.e., at an infusion rate of 210 μg/h) followed by a 35-μg/h maintenance dose was simulated according to the different models. This dosing regimen corresponds to a 0.5-μg/kg loading dose administered over 10 min and a 0.5-μg/kg/h maintenance dose for a 70-kg subject. This fixed dose was chosen for ease of interpretation, especially for those situations where body weight was included in the covariate model.

When looking at the impact of different factors on the PK profile in the first 2 h after dosing, it is clear that age, plasma albumin concentration, and body size (fat-free mass or total body weight) could have a significant impact on the early time course of dexmedetomidine plasma concentrations, particularly maximum plasma concentrations (C_{max}). For age, there appears to be some discussion, with almost no impact according to the model by Iirola et al., a negative correlation according to Lee et al. and a positive correlation between C_{max} and age according to Kuang et al. Results are more consistent for plasma albumin and body size. For the former, a positive correlation is seen, for the latter a

Table 1 Overview of published population pharmacokinetic dexmedetomidine (DMED) models in the adult population

Study (year)	Population	*N*	Blood PK samples		Patient characteristics Age/WGT/HGT average (range)	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)					
Dyck (1993) [21, 108]	Male HV	10 + 6	14 a samples after different target plasma concentrations	120 min	31.5 years (27–40) 82 kg (71–98)	TCI (based on PK parameters from first 10 subjects) targeting 0.49, 0.65, 0.81, and 0.97 ng/mL	Age, WGT, HGT	3-compartment model with HGT as a covariate on CL	Data were pooled and fitted using ELS non-linear regression; the authors suggest DMED-induced changes in SVR and CO, leading to a non-linearity in DMED PK (with higher CL at lower DMED targets)
Talke (1997) [38]	Female postoperative patients	8	14 a samples during ($n = 4$) and after ($n = 10$) DMED infusion	180 min	36 years (23–44) 69 kg (62–79) 166 cm (157–178)	TCI (based on a combination of previously published PK data) targeting 0.60 ng/mL for 60 min	Age, WGT, HGT	2-compartment model with no significant influence of tested covariates	A general overshoot of the DMED target. This is likely owing to the concomitant intra-operative use of other anesthetics
Dutta (2000) [26]	Male HV	10	22 v samples during ($n = 14$) and after ($n = 8$) DMED infusion	240 min	24 years (20–27) 78 kg (68–89) 177 cm (170–185)	CCIP (based on an unpublished two-compartment PK model) targeting 7 different plasma DMED target concentrations, resulting in measured DMED concentrations from 0.7 to 14.7 ng/mL	CO	2-compartment model with CO as covariate on CL	CO and DMED clearance were found to decrease with increasing DMED concentrations. An estimated reduction in CO and DMED CL of 19 and 12% was found at 1.2 vs. 0.3 ng/mL. The I_{max}, IC_{50}, and gamma of this inhibition were estimated separately as 0.34, 1.3 ng/mL, and 3.0, respectively. The authors found no statistically significant difference in the weighted sum of squares between a CO-dependent and a CO-independent model. The former was parameterized according to the well-stirred liver model
Venn (2002) [22]	Postoperative ICU patients	10	25 a samples during ($n = 13$) and after ($n = 12$) DMED infusion	720 min	68 years (35–80)	2.5 μg/kg/h for 10 min followed by a 0.7 μg/kg/h for 660 min (median) Average measured C_{max} is 1.12 ng/mL		2-compartment model with no tested covariates reported	

Table 1 continued

Study (year)	Population	*N*	Blood PK samples		Patient characteristics Age/WGT/HGT average (range)	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)					
Lin (2011) [39]	Chinese postoperative patients	22	24 v samples during ($n = 10$) and after ($n = 14$) DMED infusion	720 min	46 years (22–69) 60 kg (46–78) 165 cm (155–178) 13 were male, 9 were female	6 μg/kg/h loading dose for 10 min followed by 0.4 μg/kg/h maintenance dose for 350 min. Highest measured DMED concentration is approximately 1.7 ng/mL	Age, WGT, HGT, sex, BSA, BMI, LBM	3-compartment model with HGT as a covariate on CL	The authors hypothesize that the difference in V_1 with respect to the Dyck model might be owing to the venous blood sampling in this study (as compared with the arterial blood sampling in the Dyck model) Furthermore, the authors suggest that ethnic differences might be responsible for the discrepancy with earlier published PK models (no evidence/specific rational is provided for this hypothesis)
Iirola (2012) [32]	ICU patients	21	a samples during loading dose ($n = 10$) and during (every 6–8 h) DMED maintenance infusion	0 min	60 years (22–85) 85 kg (53–120) 174 cm (160–181) ALB: 13.5 (6.6–30.3)	3–6 μg/kg/h for 10 min followed by 0.1–2.5 μg/kg/h for 96 h (median in study; range: 20–571). Highest measured DMED concentration is approximately 7 ng/mL	Age, WGT, HGT, sex, BMI, LBM	2-compartment model with age as a covariate on CL and ALB on V_2	Lack of identification of "third" compartment likely owing to limited availability of samples after termination of the DMED infusion Authors warn for potential confounding by the large number of concomitant drugs that were used throughout the study
Lee (2012) [29]	Korean HV	24	13 a/v samples during ($n = 4$) and after ($n = 9$) DMED infusion	720 min	27 years (median) 71 kg (median) 174 cm (median)	3 μg/kg/h for 10 min followed by 0.17 μg/kg/h for 50 min 6 μg/kg/h for 10 min followed by 0.34 μg/kg/h for 50 min 3.7 μg/kg/h for 35 min followed by 0.7 μg/kg/h for 25 min Average measured C_{max} 1.08 and 3.3 ng/mL for lowest and highest dose group, respectively	Age, WGT, HGT, serum creatinine, AST, ALT, ALB	2-compartment model with ALB as a covariate on clearance and age on V_1	Very similar to other HV data. Authors suggest that there is little evidence to support an ethnic difference in pharmacokinetics for DMED

Table 1 continued

Study (year)	Population	*N*	Blood PK samples		Patient characteristics Age/WGT/HGT average (range)	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)					
Välitalo (2013) [24]	Critically ill patients (3 phase III trials)	527	a/v samples taken during (every 24 h) and after ($n = 2$) DMED infusion	48 h	62 years 80 kg 65% were male ALB: 23.4 g/L	0.7 µg/kg/h infusion for 1 h; afterwards titration to RASS 0 to −3 (dose levels ranging from 0.2 to 1.4 µg/kg/h) Average treatment duration: 2 days 14 h. Most measured DMED concentrations <5 ng/mL	Age, WGT, creatinine clearance, bilirubin, AST, ALT, ALB	1-compartment model with weight as a covariate on clearance and ALB on V_1	Most/all patients were mechanically ventilated. The analysis found no relationship between C_{ss} and CL. Sparse sampling could have precluded the identification of the non-linearity in DMED clearance as a function of DMED concentrations (C_{ss} at the highest DMED infusion was well below the IC_{50} reported by Dutta et al.; 2.3 vs. 1.3 ng/mL)
Cortínez (2015) [40]	Obese and non-obese laparoscopic surgery patients	20 obese/ 20 non-obese	21 v samples during ($n = 10$) and after ($n = 11$) DMED infusion	360 min	34/40 years 115/75 kg 165/166 cm	0.5 µg/kg/h for 10 minutes followed by 0.25 µg/kg/h or 0.5 µg/kg/h	Age, WGT, FFM, normal fat mass, intra-operative	2-compartment model with FFM as a covariate on clearance, Q_2, V_1 and V_2. With FAT as a covariate on clearance and intra-operative state as a covariate on V_1 and V_2	DMED was administered at the same time as propofol and remifentanil. According to the authors, TBW-based dosing is responsible for an overshoot in the obese. This is because of a lack of an effect of TBW on V_1 and V_2 and an inhibition of DMED CL as a function of fat mass. However, the authors found that during surgery the DMED V_1 is significantly lower (20.8%) which, according to the authors, is likely the result of the concomitant use of other anesthetics
Hannivoort (2015) [42]	HV	18 × 2 sessions	14 a samples during ($n = 7$) and after ($n = 7$) DMED infusion	300 min	20–70 years (range) 51–110 kg (range) 9 were male, 9 were female Age-stratified cohorts (18–34/ 35–54/ 55–72 years)	TCI (based on the model from Dyck et al.) targeting 1, 2, 3, 4, 6, and 8 ng/mL 10 min after a short (20 s) bolus infusion at 6 µg/kg/h	Age, WGT, HGT, BMI, sex	3-compartment model with weight as a covariate on clearance, Q_2, Q_3, V_1, V_2, and V_3	The authors found no systematic difference in V_1 between a volunteer's first or second session. Nevertheless, the magnitude of the IOV far exceeds the magnitude of the IIV for DMED V_1

Table 1 continued

Study (year)	Population	*N*	Blood PK samples		Patient characteristics Age/WGT/ HGT average (range)	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)					
Kuang (2016) [41]	Chinese patients under spinal anesthesia	19 young/ 16 elderly	15 a/v during ($n = 5$) and after ($n = 10$) DMED infusion	600 min	33 vs. 69 years 71 vs. 54 kg 172 vs. 158 cm ALT 49 vs.20 U/L Male:female 7:12 vs. 15:1	3.0 μg/kg/h for 10 min followed by 0.5 μg/kg/h for 50 min Maximum measured DMED concentration is approximately 1.7 ng/mL	Age, WGT, HGT, sex, BMI, AST, ALT, creatinine clearance	3-compartment model with ALT as a covariate on clearance, age on V_1 and weight on V_2	

ALB albumin, *ALT* alanine transaminase, *AST* aspartate transaminase, *BMI* body mass index, *BSA* body surface area, *CL* clearance, C_{max} maximum plasma concentration, *CO* cardiac output, C_{ss} plasma concentration at steady state, *ELS* extended least squares, *FAT* fat mass, *FFM* fat-free mass, *HGT* height, *HV* healthy volunteers, IC_{50} half maximal inhibitory concentration, *IIV* inter-individual variability, I_{max} maximal inhibition, *IOV* inter-occasion variability, *LBM* lean body mass, *N* number of subjects, *PK* pharmacokinetic, *Q* inter-compartmental clearance, *SVR* systemic vascular resistance, *TBW* total body weight, *TCI* target-controlled infusion, *V* apparent volume of distribution, *WGT* weight

negative correlation is found, i.e., a higher total body weight or fat-free mass results in a lower C_{max}.

When the predicted steady-state concentrations (C_{ss}) are compared, it appears that age, plasma albumin, height, and total body weight could be of importance (see Fig. 1). According to Iirola et al. 80-year-old patients have a significantly reduced dexmedetomidine clearance compared with 20-year-old patients, resulting in a 2.1-fold higher C_{ss}. However, when age was tested by other investigators in Asian [39] as well as non-Asian populations [21, 24, 32, 38, 40, 42], it was never retained in the final covariate model. Current evidence thus suggests it is unlikely that age has a significant influence on dexmedetomidine pharmacokinetics. Similar reasoning applies to the effect of albumin and height on C_{ss}, reported by Lee et al. and Lin et al., respectively. Moreover, the Lee albumin model goes against the broadly accepted theoretical principles of the well-stirred liver model. This theoretical framework defines that for drugs with a high hepatic extraction ratio, such as dexmedetomidine, hepatic drug clearance is independent of the fraction unbound and the serum albumin concentration but is governed primarily by hepatic blood flow. Overall, it seems unlikely that plasma albumin or height have a clinically meaningful influence on C_{ss}.

More evidence, however, is found for the influence of body weight on dexmedetomidine C_{ss}. The model of Hannivoort et al. and that of Välitalo et al. use (compartmental) allometric scaling to explain differences in dexmedetomidine clearance between individuals with a different body weight. Both models demonstrate a significant impact on C_{ss} across the evaluated body weight range with a predicted C_{ss} that is 2.3-fold higher for subjects weighing 40 kg compared with similar subjects weighing 120 kg. Cortínez et al. also used allometric scaling, albeit using a different body size descriptor, i.e., fat-free mass, to explain the inter-individual variability in dexmedetomidine clearance between lean and obese patients. Using this model, for non-obese as well as obese patients, the expected difference in C_{ss} is significant, with a 1.5-fold difference between patients with a fat free mass of 40 vs. 80 kg.

In contrast to the aforementioned PopPk models, which were based on a compartmental model with linear elimination from the central compartment, Dutta et al. found that dexmedetomidine clearance behaves non-linearly. These authors suggest that via dexmedetomidine-induced changes in cardiac output, dexmedetomidine clearance decreases 34% between ±0.3 and ±3.0 ng/mL. This observation is in good agreement with the well-stirred liver model. Nevertheless, this finding was only confirmed in the study of Iirola et al. None of the other investigators reported this non-linearity, thereby casting some doubt on

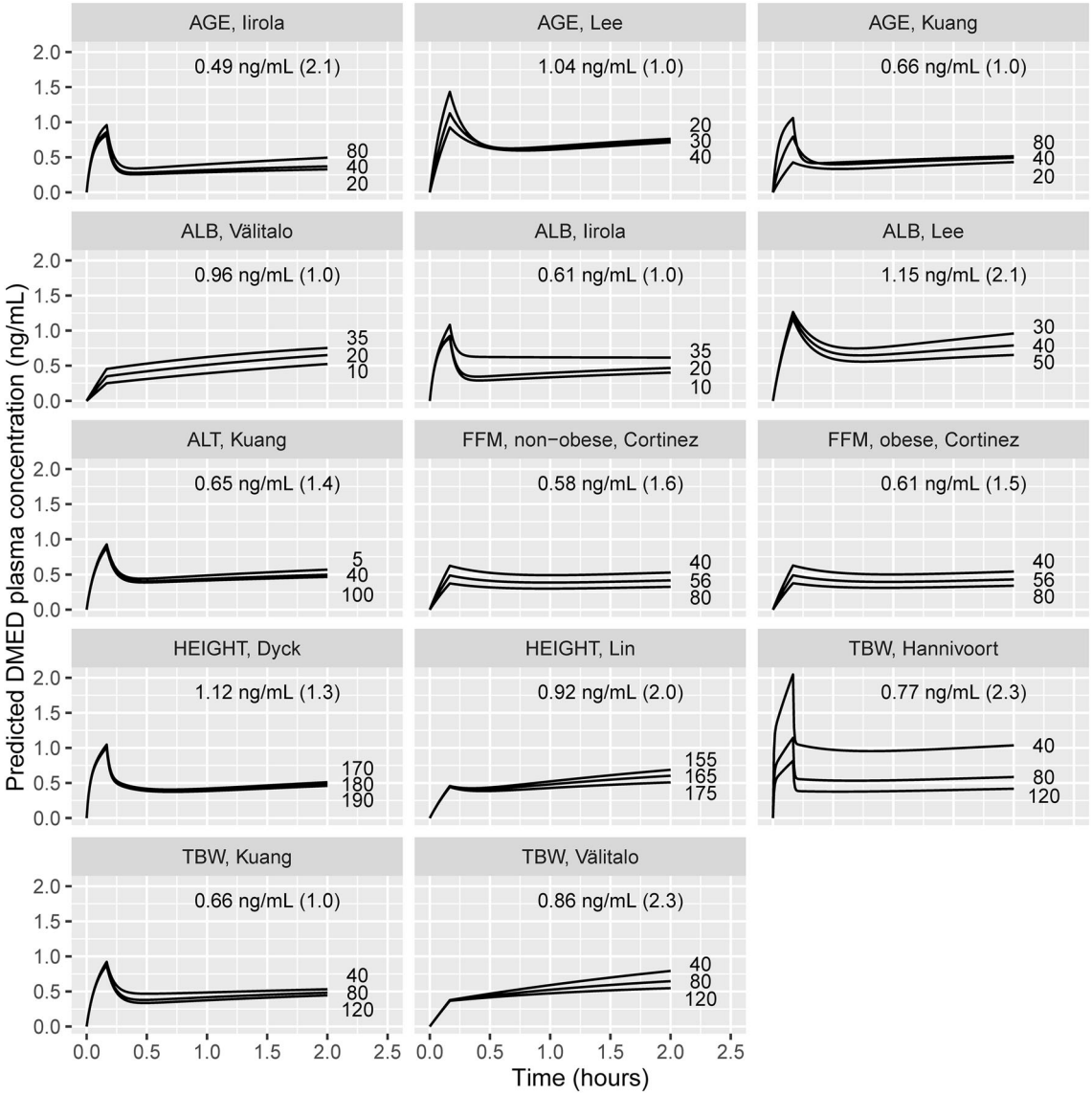

Fig. 1 Simulated concentration time profiles according to the different reported adult population pharmacokinetic models. A 35-µg loading dose infused over 10 min (i.e. at an infusion rate of 210 µg/h), followed by a 35-µg/h maintenance dose was simulated to illustrate the impact of the different covariates on the concentration time profile in the first 2 h after dosing. In addition, on the *top* of each graph the predicted dexmedetomidine (DMED) plasma concentration at steady state is shown for the typical patient with, *between parentheses*, the expected fold-difference in the C_{ss} for patients with a covariate at opposite sides of the studied covariate range. *ALB* albumin, *ALT* alanine aminotransferase, *FFM* fat free mass, *TBW* total body weight. Created with R® (R foundation for statistical computing, Vienna, Austria)

the validity and impact of this finding for dexmedetomidine pharmacokinetics.

At present, the published PopPK models for dexmedetomidine show that body size (total body weight or fat-free mass) has a significant impact on C_{max} as well as C_{ss} and should therefore be taken into account when considering dexmedetomidine administration. Plasma albumin and cardiac output are suggested to have an influence C_{max} and C_{ss}, respectively, but the evidence and impact is unclear. Otherwise, evidence in favour of an influence of other patient characteristics is diffuse and inconclusive.

5.2 Pediatric Population

Potts et al. [43] and Wiczling et al. [44] studied the pharmacokinetics of dexmedetomidine in pediatric intensive care patients, whereas Su [45, 46] and Liu [47] studied pediatric cardiac or general surgery post-operative patients. Only Su [45] evaluated the PopPK of dexmedetomidine in a neonatal population, i.e., 23 cardiac post-operative patients with ages ranging from 1 to 24 days. In all these studies, dexmedetomidine was delivered via a combination of a short (5 or 10 min) loading dose followed by a

maintenance dose. Loading doses were infused at between 0.25 and 6 μg/kg/h and maintenance doses ranged from 0.2 to 1.4 μg/kg/h or were individualized to achieve a Cook scale between 7 and 14 points [44]. For a complete overview the reader is redirected to Table 2.

All authors found that a two-compartment linear model was superior to a one- or three-compartment model for describing dexmedetomidine pharmacokinetics. In these pediatric PopPK models, most attention was directed towards identifying the relationship between body size and drug clearance and whether or not, in addition to the body size effect, significant age-related differences were present. The models are all based on allometric scaling and describe changes in clearance and volume parameters using total body weight raised to a power of 0.75 for clearance terms and 1 for volume terms. Su et al. [45] reported that a linearly scaled model (i.e., all exponents being 1) performed similarly to the allometric model. However, this was likely owing to the limited range of body weights of patients included in that study.

Three out of five studies report significant maturation effects with dexmedetomidine clearance [43–45]. However, the magnitude and maturation profiles differ between models. On the one hand, Potts et al. and Wiczling et al. found that clearance at birth was approximately 43% of adult values and matures with a half-time of 44.5 weeks to reach 84.5% of the adult clearance by 1 year of age. On the other hand, Su et al. found that a typical full-term newborn has a clearance of approximately 54% of adult values and that this clearance matures with a half-time of ±0.14 weeks to reach adult levels by 1 month of age. Su et al. suggested that their study, and not the study by Potts, has the appropriate power to reliably detect these maturational changes because of the inclusion of a cohort of pediatric patients aged younger than 1 month. Apart from the controversy between these reported maturational changes, it is clear that in all studies the magnitude of the inter-individual variability in clearance is substantially greater than the effect of maturation. Thus, from a population point of view, it is difficult to target a specific dexmedetomidine plasma concentration in a pediatric patient, regardless of age.

Overall, it seems that allometric scaling can be used to predict dexmedetomidine pharmacokinetics in children aged 1 year and older, which is in line with the findings in adults. However, for younger children this is less clear. Similar to the situation for the adult PopPK models, a uniform model based on an aggregated dataset, in combination with more data on neonatal dexmedetomidine pharmacokinetics, could provide better insight into the age-related changes that govern dexmedetomidine clearance.

To produce better insights into the characteristics governing dexmedetomidine disposition and elimination in a wide-ranged population, a uniform model based on an aggregated dataset consisting of all mentioned studies should perhaps be developed. This approach has been successfully applied in the past for propofol (cfr. the openTCI website at opentci.org), leading to the general purpose PK model for propofol [48] and has the potential to deliver a more broadly supported PopPK model for dexmedetomidine.

6 Pharmacodynamics

6.1 Sedative Effects

Sedation with dexmedetomidine resembles natural sleep and mimics the deep recovery sleep that is seen after sleep deprivation [49, 50]. Sedative and hypnotic effects of dexmedetomidine are thought to be mediated through activation of central pre- and postsynaptic α_2-receptors in the locus coeruleus and dexmedetomidine is thought to influence endogenous sleep-promoting pathways [51, 52]. The exact mechanisms are not fully understood at the moment, although it is known that receptors, other than those acting on the gamma-aminobutyric acid system, play a role [53–56].

The sedative effect of dexmedetomidine is concentration dependent, with plasma concentrations between 0.2 and 0.3 ng/mL resulting in significant and rousable sedation. Unarousable deep sedation is thought to occur at plasma concentrations above 1.9 ng/mL [9, 57].

6.1.1 Intensive Care Unit Sedation and Delirium

Although the US Food and Drug Administration approved dexmedetomidine for use up to 24 h only, multiple studies showed an acceptable safety profile when using continuous dexmedetomidine sedation up to 30 days in ICU patients [58, 59]. In the MIDEX ($n = 500$) and PRODEX ($n = 498$) trials [59], sedative properties of midazolam and propofol were compared with dexmedetomidine (<1.4 μg/kg/h) in mechanically ventilated adult ICU patients. In providing light to moderate sedation, dexmedetomidine was found not to be inferior to midazolam or propofol. Furthermore, a shorter time to extubation was observed with dexmedetomidine. A Cochrane review covering seven studies and 1624 participants [60], compared long-term use of dexmedetomidine in ICU sedation with traditional sedatives. Dexmedetomidine reduced duration of mechanical ventilation by 22% and length of ICU stay by 14%. No differences in mortality were found.

It is hypothesized that sedation with dexmedetomidine results in a more physiologic sleep-wake cycle and patients remain rousable and cooperative, thereby reducing the risk

Table 2 Overview of published population pharmacokinetic dexmedetomidine (DMED) models in the pediatric population

	Population	*N*	Blood PK samples		Patient characteristics Age/WGT/HGT average (range)	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)					
Potts (2009) [43]	Pediatric ICU patients	95[a]	a (1 trial) and v (3 trials) samples during and after DMED infusion	8 h	3.83 years (0.01–14.4) 16.0 kg (3.1–58.9)	1–6 μg/kg over 5 or 10 min or 0.2-μg/kg/h infusion	Age, WGT, cardiac surgery, arterial/venous sampling, study site	2-compartment model with age, WGT (allometry) and post-cardiac surgery state as covariates on CL and WGT (allometry) as a covariate on Q_2, V_1, and V_2	IIV is almost twofold higher than the effect of maturation (30.9% vs. approximately 20%). Clearance in post-operative cardiac pediatric patients was approximately 27% reduced compared with other pediatric patients
Su (2010) [45]	Pediatric cardiac post-operative patients	36	a/v samples obtained during ($n = 5$) and after ($n = 8$) DMED infusion	24 h	7.8 months (2.6–20.4) 7.0 kg (5.1–11.9) 20 were male, 16 were female	0.35–1 μg/kg over 10 min followed by 0.25–0.75 μg/kg/h for 2–24 hours	Age, WGT, total cardiopulmonary bypass time, ventricular physiology	2-compartment model with age and ventricular physiology as covariates on CL	A full covariate model was reported. Nevertheless, only the covariate for ventricular physiology on CL had acceptable precision (i.e., RSE <50%). BSV is higher than the effect of maturation
Liu (2016) [47]	Chinese pediatric general surgery patients	39	v samples obtained during ($n = 1$) and after ($n = 12$) DMED infusion	8 h	3.0 years (1–9) 14.5 kg (10–27) 20 were male, 19 were female	1.0–2.0 μg/kg over 10 min	Age, WGT, BMI, sex, lean body mass	2-compartment model with WGT (allometry) as a covariate on CL, Q_2, V_1, and V_2	During surgery patients were maintained under anesthesia with sevoflurane, which might have caused a shift in plasma protein binding of DMED resulting in a higher distribution volume
Su (2016) [45]	Neonatal and pediatric post-operative patients	23 + 36	a/v samples obtained during and after DMED infusion[b]	18 h[b]	4.3 months (0.03–20.4) 5.9 kg (2.3–11.9) 32 were male, 27 were female	0.25–1 μg/kg over 10 min followed by 0.20–0.75 μg/kg/h for 2–24 h	Age, WGT, total cardiopulmonary bypass time, ventricular physiology	2-compartment model with age, WGT (allometry), total bypass time, and ventricular physiology as covariates on CL and WGT (allometry) as a covariate on Q_2, V_1, and V_2	WGT-corrected CL increases with age until approximately 1 month. A linearly scaled version of the model performs slightly better, probably owing to the limited WGT range of the included subjects

Table 2 continued

	Population	*N*	Blood PK samples		Patient characteristics	Drug administration	Tested covariates	Covariate models	Remarks
			No. of samples a (arterial) v (venous)	Last sample (time after termination of infusion)	Age/WGT/HGT average (range)				
Wiczling (2016) [44]	Critically ill pediatric patients	38	a samples obtained during ($n = 8$) and after ($n = 7$) long-term DMED infusion	6 h	5.8 years (0.12–15.7) 18.5 kg (4.7–60) 23 were male, 15 were female	Initiation of 0.8 µg/kg/h with titration to effect for ventilated patients with maximum of 1.4 µg/kg/h	cfr. Potts	2-compartment model with age, WGT (allometry), and fractional increase in the 2nd session as covariates on CL and with WGT (allometry) and fractional increase in the 2nd session as covariates on Q_2, V_1, and V_2	Results might be confounded by concomitant use of sufentanil and midazolam. No population PK model was developed, the parameter estimates were obtained by a Bayesian fit of the Potts model to these data. The posterior distribution for the parameters closely resembles the prior distributions

BMI body mass index, *CL* clearance, *HGT* height, *ICU* intensive care unit, *IIV* inter-individual variability, *N* number of subjects, *PK* pharmacokinetic, *Q2* inter-compartmental clearance, *RSE* relative squared error, *BSV* between subject variability, *V* apparent volume of distribution, *WGT* weight

[a] Combination of four earlier published trials

[b] Sampling schedules were adapted to the subjects WGT, samples were obtained up to 10, 12, 15, and 18 h after stopping the drug infusion

of delirium [61]. A double-blind randomized controlled trial (RCT) by Pandharipande et al. [62] in 106 mechanically ventilated patients, showed that continuous use of dexmedetomidine for up to 5 days resulted in more coma- and/or delirium-free days compared with lorazepam infusion. In the PRODEX trial, a reduced incidence of delirium was found in patients sedated with dexmedetomidine as compared with propofol. Moreover, after cardiac surgery, sedation with dexmedetomidine and fast-track weaning protocols were found to decrease the incidence of delirium [63].

6.1.2 Procedural Sedation

Dexmedetomidine was approved for procedural sedation in USA after two RCTs in 326 patients scheduled for therapeutic or diagnostic procedures and 105 patients undergoing awake fiberoptic intubation [64, 65]. In the first trial, 40 and 53% of patients did not require rescue midazolam in the dexmedetomidine groups receiving a 0.5- or 1-µg/kg loading dose, respectively, vs. 3% of patients in the placebo group [64]. In the awake fiberoptic intubation study, 52% of patients in the dexmedetomidine group did not require rescue midazolam vs. 14% of patients in the placebo group [65]. In neurosurgical procedures, cortical-evoked potentials were minimally affected by dexmedetomidine and therefore dexmedetomidine may be useful in epilepsy surgery, as epileptiform activity will not be obscured [66]. In recent years, several studies were conducted, addressing a wide range of procedures in differing populations. For a thorough review of these trials, the reader is referred to Gerlach et al. [67].

6.2 Analgesic Effects

Analgesic effects of α_2-agonists are thought to be mediated by α_2-receptor binding in central and spinal cord α_2-receptors. Pain transmission is suppressed by hyperpolarization of interneurons and reduction of the release of pronociceptive transmitters such as substance P and glutamate [52]. Studies investigating the analgesic properties of dexmedetomidine found that exposure resulting in mild to deep sedation seems to lack analgesic efficacy [53, 68]. When administered as a sole agent in healthy volunteers, dexmedetomidine in concentrations up to 1.23 ng/mL does not provide adequate analgesia to heat or electrical stimuli [53]. Furthermore, in a crossover trial comparing respiratory and analgesic effects between dexmedetomidine and remifentanil, dexmedetomidine plasma concentrations up to 2.4 ng/mL provided less effective analgesia than remifentanil. In conclusion, the analgesic effects of dexmedetomidine are still unclear and may partly be owing to an altered perception and reduced anxiety, though an

opioid-sparing effect is described and there may be an effect when used with locoregional anesthesia techniques (see also Sect. 9).

6.3 Cardiovascular Effects

Dexmedetomidine produces a typical biphasic hemodynamic response, resulting in hypotension at low plasma concentrations and hypertension at higher plasma concentrations [9, 57]. An IV bolus administration of dexmedetomidine, which results in a high (peak) plasma concentration, results in an increase in blood pressure combined with a marked decrease in heart rate. During this phase, a marked increase in systemic vascular resistance has been shown [9, 57]. This is thought to originate from α_2-receptor activation in the vascular smooth muscles, causing peripheral vasoconstriction and thereby hypertension. This is accompanied by a quick reduction in heart rate, presumably caused by the baroceptor reflex [9]. After a few minutes, when dexmedetomidine plasma concentrations decrease, the vasoconstriction attenuates, as dexmedetomidine also activates α_2-receptors in the vascular endothelial cells, which results in vasodilatation [69, 70]. Together with presynaptic α_2-adrenoreceptors inhibiting sympathetic release of catecholamines and the increased vagal activity, this results in a hypotensive phase. An average decrease, as compared with baseline, in mean arterial blood pressure of 13–27% was observed and is maintained for a prolonged period of time after the initial dose [9, 57]. A sustained dose-dependent reduction in circulating plasma catecholamines by 60–80%, as found in multiple studies, is consistent with these long-lasting sympatholytic effects of dexmedetomidine [9, 38, 57]. As with initial high plasma concentrations after an IV bolus or fast loading dose, higher maintenance doses are associated with progressive increases in MAP [9]. The hypertensive effects overcome the hypotensive effects at concentrations between 1.9 and 3.2 ng/mL [3, 9].

Transoesophagal echocardiographic evaluations in patients receiving dexmedetomidine infusions during total IV anesthesia with propofol and remifentanil did not show impaired systolic or diastolic function [71]. Cardiac output was reduced as a result of a lower heart rate. Ebert et al. who studied the effects of dexmedetomidine plasma concentrations varying from 0 to 15 ng/mL in healthy volunteers, also found that cardiac output gradually decreased with heart rate. However, no decrease in stroke volume was seen until plasma concentrations exceeded 5.1 ng/mL [9].

High dexmedetomidine plasma concentrations are associated with significant increases in systemic and pulmonary vascular resistance, resulting in pulmonary and systemic hypertension [9]. This could be a limiting factor, especially in patients with known cardiac problems, who may rely on their heart rate to provide sufficient cardiac output. If necessary, high plasma concentrations can be avoided by decreasing loading dose sizes or by increasing time over which the loading dose is administered.

6.4 Respiratory Effects

With therapeutic plasma concentrations up to 2.4 ng/mL, minimal respiratory depression is seen with a preservation of ventilatory response to CO_2 [1, 22, 72]. In a trial comparing remifentanil with dexmedetomidine in healthy volunteers, no respiratory depression in the dexmedetomidine session was observed for targeted plasma concentrations up to 2.4 ng/mL. The ventilatory frequency increased with increasing doses, which compensated for slightly decreased tidal volumes. Hypercapnic arousal phenomena, similar to those during natural sleep, were seen during dexmedetomidine sedation [72]. Even at supratherapeutic plasma concentrations (up to 14.9 ng/mL) as studied by Ebert et al., when volunteers were unarousable, respiratory drive was unaffected, leading to only slight increases in carbon dioxide levels (3–4 mmHg) and respiratory rates. However, a recently published paper by Lodenius et al. [73] does describe a significant reduction in respiratory response to hypercapnia and hypoxia in dexmedetomidine-sedated young healthy volunteers with mean plasma concentrations of around 0.66 ng/mL.

The hypercapnic ventilatory response is known to decrease with age [74]. Elderly patients are therefore more vulnerable to respiratory depression than young healthy volunteers. When co-administered with other sedative, hypnotic, or analgesic agents, an enhanced sedative effect and increased risk of ventilatory depression or apnea is reported [75]. In response to these findings, the summary of product characteristics for Dexdor was updated in 2015, stating that dexmedetomidine should only be used in an intensive care setting with continuous cardiac and respiratory monitoring.

7 Pharmacokinetic and Pharmacodynamic Interactions

7.1 Pharmacokinetic Interactions

No relevant PK interactions were observed in studies where dexmedetomidine (target concentrations ranging from 0.2 to 0.6 ng/mL) was combined with propofol, midazolam, isoflurane, or alfentanil.

Pre-clinical studies showed that the half-maximal inhibitory values (IC_{50}) for dexmedetomidine against multiple CYP isoforms are relatively high (0.65–70 μM). Because therapeutic plasma concentrations are much lower

(≤10 ng/mL or ≤0.04 μM), the sponsor expected no significant PK interactions with CYP-metabolized drugs in clinical practice [2]. However, in rats, it was shown that liver dexmedetomidine concentrations were almost 100-fold higher than plasma dexmedetomidine concentrations [28, 76]. As such, interactions, especially related to inhibition of CYP3A4, which is the isoform with the lowest IC_{50}, could become important. Since its introduction onto the market, several PK interactions have been described. In one case report, a fourfold increase in tacrolimus concentrations after the start of dexmedetomidine infusion was found and thought to originate from CYP3A4 inhibition [76].

Furthermore, it was seen that volunteers with seizure disorders using enzyme-inducing anticonvulsants ($n = 8$) had a 43% increased plasma clearance of dexmedetomidine when compared with control subjects ($n = 8$) [77]. In general, antidepressant use might be associated with alterations in the PK and/or pharmacodynamic (PD) profile of dexmedetomidine, leading to an enhanced sedative effect [78].

More research is necessary to investigate whether human liver dexmedetomidine concentrations are such that CYP3A4, or other isoforms, could be inhibited to a significant degree within the therapeutic range of dexmedetomidine plasma concentrations.

7.2 Pharmacodynamic Interactions

Dexmedetomidine reduces requirements of other anesthetics such as isoflurane [79–81], sevoflurane [82, 83], propofol [84–86], thiopental [87–90], and fentanyl [91]. Less sevoflurane was required during abdominal surgery when co-administered with dexmedetomidine (1-μg/kg loading dose and 0.5-μg/kg/h maintenance dose) [83]. Furthermore, a 21% lower sevoflurane half-maximal effective concentration (EC_{50}) for laryngeal mask insertion in children was found when premedication with dexmedetomidine 2 μg/kg was given intranasally [82].

Jang et al. [86] observed that the EC_{50} of propofol for successful laryngeal mask insertion without muscle relaxants was 3.18 μg/mL in the group receiving the 1-μg/kg dexmedetomidine premedication, compared with 6.75 μg/mL in the group receiving saline placebo. Although heterogeneity in study populations, dosing regimens, and timing of drug administration obscures the results, a reduction in the propofol requirement is found when co-administered with dexmedetomidine. With the relatively slow onset of dexmedetomidine, timing should be optimized such that peak effects of both drugs occur at the same time.

An opioid-sparing effect is described when using dexmedetomidine perioperatively [92–94]. This might be beneficial in reducing post-operative nausea or ventilatory depression as seen with opiates. A review and meta-analysis by Blaudszun et al. [95] describes a reduced post-operative cumulative opioid consumption with clonidine (−4.1 mg morphine equivalents) and dexmedetomidine (−14.5 mg morphine equivalents), 24 h after surgery. A recent Cochrane review summarizes seven studies with a total of 492 participants and addresses the opioid-sparing effect of perioperative dexmedetomidine for acute pain after abdominal surgery in adults [96]. A modest reduction in opioid consumption in the first 24 h after surgery was found, although no clinically important differences in postoperative pain were noted. Intraoperative dexmedetomidine infusion of 0.2–0.5 μg/kg/h reduced analgesic consumption after craniotomy in two RCTs with 80 and 60 patients [92, 93]. In anesthetized patients, in general, pain medication administration is often increased when heart rate and blood pressure increase. The hemodynamic effects of dexmedetomidine might confound the pain assessment and as such, be responsible for the reduced intra-operative opioid consumption.

Interactions between dexmedetomidine and antihypertensive agents were investigated as part of the registration procedure. β-Blockers might lead to an increase in hypotensive and bradycardic effects [3]. Calcium channel blockers might attenuate the changes in heart rate and blood pressure associated with dexmedetomidine infusion without an effect on plasma catecholamine levels [3].

8 Special Populations

8.1 Renally Impaired

Dexmedetomidine is mainly hepatically metabolized. Renal impairment does not influence the pharmacokinetics of dexmedetomidine to any significant extent. In one study comparing dexmedetomidine pharmacokinetics between patients with severe renal impairment (creatinine clearance <30 mL/min) and healthy volunteers, Wolf et al. [20] found no difference in either volume of distribution or elimination clearance. However, sedative effects lasted longer in patients with renal disease. This was hypothesized to originate from a lower plasma protein level and hence higher unbound drug concentrations. However, this hypothesis was negated by Karol and Maze who describe no significant differences in dexmedetomidine plasma protein binding in plasma from patients across four different renal function groups [19].

8.2 Hepatically Impaired

In hepatically impaired patients, a decreased clearance and a higher unbound fraction of dexmedetomidine were

observed. In a pre-registration study by Abbott Laboratories, mean clearance values in patients with mild, moderate, and severe hepatic impairment were 74, 64, and 53% of those found in healthy subjects. The mean elimination half-life of dexmedetomidine in healthy subjects was 2.5 h and it was prolonged to 3.9, 5.4, and 7.4 h in patients with mild, moderate, and severe hepatic impairment, respectively. These findings were similar to those reported by Cunningham et al. [97]. Dexmedetomidine plasma protein binding in patients with mild, moderate, and severe hepatic impairment was 87.9, 86.0, and 82.0% compared with 89.8% in normal subjects [19, 28]. Overall, the dosing regimen of dexmedetomidine should be reduced in patients with hepatic impairment, thereby accounting for the changes in pharmacokinetics, PD response, and the degree of hepatic impairment.

8.3 Pediatric Population

Although there is no approved indication in the pediatric population, literature reports on pediatric applications of dexmedetomidine have increased in number. In the summary of product characteristics of Dexdor, the section on pediatric pharmacology was updated in 2013, stating that dexmedetomidine in post-operative pediatric ICU patients (>1 month and <17 years) is safe and efficacious during use for up to 24 h [3, 98].

8.3.1 Children Aged 1 Month to 17 Years

In children aged older than 1 month, dexmedetomidine appeared to exhibit a level of efficacy similar to that seen in adults and to be fairly well tolerated. In young children aged 2 months to 6 years, weight-adjusted plasma clearance rates are slightly higher (0.8–1.2 L/kg/h) compared with older children and adults (0.6–0.7 L/kg/h) [42, 43]. A study with mainly post-operative pediatric ICU patients older than 1 month, demonstrated a similar safety profile as compared with the adult population. Loading doses of 0.5–1.0 μg/kg over 10–20 min were studied. In a study with 669 pediatric subjects (0.1–22.5 years), dexmedetomidine was effective in providing sedation during nuclear medicine imaging without a detrimental effect on respiration. Hemodynamic adverse effects occurred more often in older children but did not require any pharmacologic intervention [99].

8.3.2 Neonates

Neonates form a special population where immaturity of hepatic metabolism affects pharmacokinetics (see Sect. 5.2 and Table 2) [100–102]. In neonates, body composition, fat distribution, and lower protein and albumin levels may contribute to a larger volume of distribution and an increased elimination half-life. Furthermore, an immature blood–brain barrier may cause higher cerebrospinal fluid concentrations with increased sedative and analgesic effects [103]. Chrysostomou et al. [104] investigated dexmedetomidine pharmacokinetics in 24 term (36–44 weeks) and 18 preterm (28–36 weeks) neonates. Preterm neonates had lower weight-adjusted plasma clearance (0.3 vs. 0.9 L/h/kg) and an increased elimination half-life (7.6 vs. 3.2 h) than term neonates. Premature neonates were adequately sedated with dexmedetomidine alone, although doses up to 0.2 μg/kg/h were not sufficient in most term neonates. For an overview of available models that describe the maturation of the clearance in neonates, the reader is redirected to Sect. 5.2.

Most side effects of dexmedetomidine are related to sympatholytic effects and appear to be dose dependent and predictable in neonates. With the relatively low doses studied by Chrysostomou et al., no significant hemodynamic and respiratory changes were found [104]. One case of hypothermic bradycardia in a neonate has been reported [105]. Thermoregulation in neonates depends primarily on vasoconstriction and non-shivering thermogenesis by lipolysis. As these mechanisms are both affected by dexmedetomidine, neonates are particularly vulnerable for hypothermia [106, 107].

8.4 Elderly

In multiple PK studies, age does not clearly influence the PK profile of dexmedetomidine [2, 42, 108]. In a pre-registration phase I study in 60 healthy volunteers, after bolus administration of 0.6 μg/kg dexmedetomidine over 10 min, no difference in dexmedetomidine pharmacokinetics was seen between groups aged 18–40 years ($n = 20$), 41–65 years ($n = 20$), and older than 65 years ($n = 20$) [28].

In the elderly, sedative effects seem to be more pronounced. Lower doses of dexmedetomidine were needed to provide adequate sedation in elderly patients (aged 65–78 years) as compared with younger patients (aged 45–64 years) [109]. In another study, excessive sedation occurred in 46 and 60% of elderly patients (aged >60 years) receiving 0.5 and 1 μg/kg dexmedetomidine, respectively, [110]. In a study by Ko et al. [111], loading doses of 0.1–1.0 μg/kg over 10 min were well tolerated in 47 elderly subjects (aged >65 years). Hypotension was observed more frequently in patients receiving loading doses of ≥0.7 μg/kg. The registration documents of the Food and Drug Administration and European Medicines Agency report a higher incidence of bradycardia and hypotension in patients aged older than 65 years [2, 3]. Age-adjusted dosing is not recommended, although caution

is warranted as hemodynamic and sedative effects might be more pronounced in elderly patients who are often have multiple co-morbidities.

8.5 Obese

Obese patients are prone to obstructive apnea and opioid-related ventilatory depression. Therefore, several studies were performed regarding the use of dexmedetomidine as an anesthetic adjunct in morbidly obese patients undergoing bariatric surgery [112–115]. Tufanogullari et al. [113] studied doses up to 0.8 μg/kg/h in a total of 80 patients. In dexmedetomidine groups, end-tidal desflurane concentrations were reduced by 19–22%. In the post-anesthesia care unit, patients in the dexmedetomidine groups needed less rescue fentanyl, less anti-emetic therapy, and had a shorter length of stay. A dose of 0.2 μg/kg/h appeared to be effective while minimizing cardiovascular side effects. In another study, a dexmedetomidine 0.8-μg/kg bolus was followed by a 0.4-μg/kg/h continuous infusion and compared with placebo in a total of 80 patients [112]. Decreased amounts of fentanyl and propofol were required for maintenance anesthesia and more stable hemodynamics were described, whilst postoperative pain and total amount of morphine were decreased. Feld et al. [114] compared dexmedetomidine with fentanyl as an adjunct to desflurane anesthesia and concluded that dexmedetomidine use decreased heart rate, blood pressure, desflurane requirements, post-operative pain level, and morphine use in the post-anesthesia care unit compared with fentanyl.

9 New Clinical Applications

Various interesting off-label applications of dexmedetomidine have been investigated over the past few years.

9.1 Prevention of Emergence Agitation

A recent meta-analysis [116] including 19 randomized controlled trials compared dexmedetomidine with other regimens in preventing post-operative emergence agitation in children aged 0–18 years. This meta-analysis concluded that dexmedetomidine was more effective than placebo, propofol, and remifentanil in preventing emergence agitation. Effectiveness was similar to that of ketamine and midazolam. One RCT addressed this subject in 115 elderly (aged >65 years) patients undergoing orthopedic surgery. They more frequently found a calm state at emergence in groups receiving dexmedetomidine compared with placebo, as an adjuvant to total IV or sevoflurane anesthesia [117].

9.2 Intranasal Use

The intranasal route is the most used extravascular route of administration of dexmedetomidine in clinical practice. It can be useful for sedation and premedication in pediatric subjects [18, 118–120]. After an intranasal dose of 84 μg dexmedetomidine in healthy volunteers, a lag time of 2–3 min was described and the time to maximum plasma concentration was reached 38 min after administration. Bioavailability was found to be 82% [16, 17]. In another study, intranasal doses of 1–4 μg/kg dexmedetomidine were investigated in healthy volunteers and children. Significant sedation, with an onset time of 15–45 min, was observed for 1–2 h and was well tolerated [118, 121–123]. Moreover, 1–2 μg/kg intranasal dexmedetomidine was found to attenuate the stress response caused by intubation in children [124]. Premedication with intranasal dexmedetomidine also reduced the minimum alveolar concentration of sevoflurane needed for laryngeal mask insertion or tracheal intubation [82, 125, 126].

Recently, Li et al. [18] compared 3 μg/kg intranasal dexmedetomidine, administered by atomizer or drops in 279 children under 3 years of age. Both were equally effective. A disadvantage for intranasal dexmedetomidine when compared with midazolam or ketamine is the relatively slow onset of effect [119, 120]. When comparing IV 1 μg/kg dexmedetomidine with intranasal 1 μg/kg dexmedetomidine, onset times were 15–20 and 30–45 min, respectively [127]. Further research regarding the efficacy, safety, and tolerability in elderly subjects as well as studies regarding optimal timing and dosing regimens are required.

9.3 Patient-Controlled Analgesia

Opioid-dexmedetomidine combinations for post-operative, patient-controlled analgesia systems are being evaluated. A meta-analysis of seven randomized controlled trials concluded that this combination is safe and effective [128]. When compared with an opioid alone, lower post-operative pain intensity scores, lower incidence of post-operative nausea and vomiting, lower morphine-equivalent consumption, and a higher patient satisfaction were found. An opioid-sparing effect might be beneficial for patients at risk for post-operative nausea and vomiting or respiratory depression.

9.4 Prolongation of Spinal or Peripheral Nerve Blocks

α_2-Agonists are frequently used as an adjuvant to prolong duration of spinal or peripheral blocks [129, 130]. In a meta-analysis by Abdallah et al. [131], it was found that IV dexmedetomidine interacts synergistically with regional

anesthesia. It prolonged the duration of sensory block by at least 34%, motor block by at least 17%, and it prolonged the time to first analgesic request by at least 53%. Prolonged analgesic duration was also described in a systematic review on the perineural use of dexmedetomidine by Wu et al. [132]. A recent RCT by Abdallah et al. [129] compared perineural and IV dexmedetomidine with placebo as adjuvant to interscalene plexus blocks. The duration of analgesia was 10.9, 9.8, and 6.7 h in the perineural dexmedetomidine, IV dexmedetomidine, and placebo groups, respectively. The authors concluded that both IV and perineural dexmedetomidine can effectively prolong interscalene block analgesia without prolonging motor blockade.

Although the exact mechanisms of action are unclear, these effects are thought to occur partly through local perineural mechanisms with prolonged hyperpolarization of sensory C fibers and, to a lesser degree, the motoric A fibers. Direct central effects on the locus coeruleus seem to play a role as well [5, 52, 129].

9.5 Organ Protective Properties

α_2-Receptors are found in multiple organs such as the liver, lungs, kidneys, and brain. In animal studies, dexmedetomidine appears to attenuate renal inflammation responses and ischemia reperfusion injury [133, 134]. In addition, neuro- and cardioprotective properties have been described. Several mechanisms are reported to be involved, such as activation of pro-survival kinases [135], modification of oxidative and inflammatory responses [136], and activation of the endothelial nitric oxide synthase [137]. In animal studies, it was found that dexmedetomidine potentially protects against neuro-apoptosis caused by other agents [138–140]. This contrasts with frequently used drugs such as opioids and benzodiazepines, which can cause neurodevelopmental abnormalities in neonatal animals. Moreover, improved neurologic outcome and attenuated cerebral necrosis were found in animal models of induced cerebral ischemia and reperfusion [141]. These neuroprotective properties are thought to originate from a reduced cerebral catecholamine and glutamate release and modulation of apoptosis-regulating proteins [141, 142].

9.6 Antagonists

Two major limitations regarding dexmedetomidine use are its long-lasting effects and its hemodynamic side effects. A safe and quick reversal of these effects would benefit clinical practice, presumably leading to a more widespread use of dexmedetomidine. The selective α_2-antagonist atipamezole can effectively reverse dexmedetomidines hemodynamic and sedative effects [143–145]. The reduction in heart rate and blood pressure caused by dexmedetomidine is quickly reversed after IV administration of 15–150 μg/kg atipamezole. Higher doses of atipamezole (150 μg/kg) also reverse sedation. Transient orthosympathic activation, with a 10-fold increase in plasma norepinephrine levels is seen with higher doses or fast infusion rates [143]. However, atipamezole is currently only used in veterinary medicine and is not approved for use in humans.

10 Conclusions

Dexmedetomidine is an efficacious and safe drug used to sedate patients in the ICU and/or during procedural sedation. Its PK and PD properties have been studied extensively, both within and beyond the scope of the currently approved indications. Dexmedetomidine exposure is mainly governed by its hepatic clearance. Hepatic impairment was shown to have an impact on the pharmacokinetics and should therefore be taken into account when choosing a dosing regimen. From the reported PK studies, it seems that the bodyweight-adjusted dosing that is currently applied is only justified for non-obese patients. For obese patients, other body size descriptors, e.g., fat-free mass, are potentially more appropriate. Evidence in favour of the influence of other patient characteristics, such as plasma albumin levels, cardiac output, and age is less convincing. Furthermore, at the moment, much uncertainty remains on the maturation of the hepatic clearance in neonates/children and therefore thoroughly validated age-based dosing regimens are lacking.

The sedative, analgesic, and cardiovascular effects of dexmedetomidine are well described. Nevertheless, at the moment, quantitative PK/PD models, which could help to delineate the variability in the observed effects, are not available. Respiratory depression is unlikely when dexmedetomidine is used alone. However, recent reports suggest that when it is combined with other sedatives or hypnotics, there is an increased risk, necessitating continuous respiratory monitoring. Other PD interactions as well as PK interactions have been described. Some of these, e.g., the opioid-sparing effect, are studied as new treatment modalities but more research is needed to better characterize the underlying mechanisms.

Compliance with Ethical Standards

Funding Only departmental funding was used to assist with the preparation of this review.

Conflict of Interest Maud A. S. Weerink, Laura N. Hannivoort, Clemens R. M. Barends, and Pieter Colin have no conflicts of interest to declare. Michel M. R. F. Struys's research group/department

received grants and funding from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), and Medtronic (Dublin, Ireland); and he has received honoraria from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Baxter (Deerfield, IL, USA), Medtronic (Dublin, Ireland), and Demed Medical (Temse, Belgium). Anthony R. Absalom's research group/department received grants and funding from The Medicines Company (Parsippany, NJ, USA), Masimo (Irvine, CA, USA), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, The Netherlands), and Medtronic (Dublin, Ireland); and he has received honoraria from The Medicines Company (Parsippany, NJ, USA) and Janssen Pharmaceutica NV (Beerse, Belgium).

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