

Supplementary Information for:

Best evidence-based dosing recommendations for dexmedetomidine for premedication and procedural sedation in pediatrics: outcome of a risk-benefit analysis by the Dutch Pediatric Formulary

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Pediatric Drugs, 2022

Content:

Online Resource 1 – Pubmed search query

Online Resource 2 – Risk benefit analysis

Online Resource 3 – Literature grading system

Online Resource 1 – Pubmed search query

Search 1. All studies on dexmedetomidine in pediatrics

dexmedetomidine* [Title] **AND** (Pediatrics[mh] OR Child[mh] OR Infant[mh] OR Infan*[tiab] OR Newborn*[tiab] OR "New-born*" [tiab] OR Perinat*[tiab] OR Neonat*[tiab] OR Baby*[tiab] OR Babies[tiab] OR Prematur*[tiab] OR Preterm*[tiab] OR Toddler*[tiab] OR Minors*[tiab] OR Boy[tiab] OR Boys[tiab] OR Boyfriend[tiab] OR Boyhood[tiab] OR Girl*[tiab] OR Kid[tiab] OR Kids[tiab] OR Child*[tiab] OR Schoolchild*[tiab] OR "School child*" [tiab] OR Juvenil*[tiab] OR Youth*[tiab] OR Teen*[tiab] OR "Under age*" [tiab] OR Pubescen*[tiab] OR Pediatric*[tiab] OR Pediatric*[tiab] OR Pediatric*[tiab] OR School*[tiab])
→ 951 results (18 Jan 2021)

Search 2. Select meta-analyses and systematic reviews

dexmedetomidine* [Title] **AND** (Pediatrics[mh] OR Child[mh] OR Infant[mh] OR Infan*[tiab] OR Newborn*[tiab] OR "New-born*" [tiab] OR Perinat*[tiab] OR Neonat*[tiab] OR Baby*[tiab] OR Babies[tiab] OR Prematur*[tiab] OR Preterm*[tiab] OR Toddler*[tiab] OR Minors*[tiab] OR Boy[tiab] OR Boys[tiab] OR Boyfriend[tiab] OR Boyhood[tiab] OR Girl*[tiab] OR Kid[tiab] OR Kids[tiab] OR Child*[tiab] OR Schoolchild*[tiab] OR "School child*" [tiab] OR Juvenil*[tiab] OR Youth*[tiab] OR Teen*[tiab] OR "Under age*" [tiab] OR Pubescen*[tiab] OR Pediatric*[tiab] OR Pediatric*[tiab] OR Pediatric*[tiab] OR School*[tiab])
+ use filter: "meta-analysis and systematic reviews, sort on: date → 48 results (22 Jan 2021)

Online Resource 2 – Risk-benefit analysis

Dutch Pediatric Formulary: Dexmedetomidine

Starting point (September-2020): Despite increased use of dexmedetomidine in pediatrics a monograph on the use of the drug is missing in the Dutch Pediatric Formulary. It was suggested to provide dosing recommendations for both IV and intranasal use. The indications suggested include among others: premedication, mild sedation during short painful procedures (in combination with local analgesia), during EEG and during long-term imaging (instead of anaesthesia or deep sedation during MRI). Only include dosing recommendations for IV and/or intranasal administration, not other routes (epidural, inhalation, intramuscular, oral, sublingual) as these are not common in pediatric care NL.

Date literature search: September 2020

1. Registration information

Source	Evidence	Effect	Remarks
Ref. 1a Dexmedetomidine Accord 21-07-2020	SmPC	4.2 The safety and efficacy of dexmedetomidine in children aged 0 to 18 years have not been established. No recommendation on a posology can be made. Adults: Sedation on the ICU: already intubated and sedated patients can be converted to dexmedetomidine with an initial infusion of 0.7 µg/kg/h after which the dose is adjusted to 0.2-1.4 µg/kg/h based on effect. Max. 1.4 µg/kg/h. Loading dose not recommended	On NL market since June 2011. In adults, used for indication: 1) sedation of ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation 2) sedation of non-intubated patients prior to and/or during diagnostic or surgical procedures
Ref. 1b Dexdor 29-05-2020			
Ref. 1c Dexmedetomidine Altan 07-02-2020			
Ref. 1d Dexmedetomidine EVER 26-03-2020			
Ref. 1e Dexmedetomidine Kalceks 17-07-2020			
		4.8 Children >1 month postnatal, predominantly post-operative, have been evaluated for treatment up to 24h in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (GA: 28-44 weeks) is very limited and restricted to maintenance doses ≤ 0.2 µg/kg/h.	

Source	Evidence	Effect	Remarks
Ref. 1f Dexmedetomidine Teva 11-03-2020		5.1 Post-operative dexmedetomidine is considered effective and safe in children of 1 month to ≤17 years, for up to 24h. Data on treatment >24h is not available. New-born infants may be particularly sensitive to the bradycardic effects of dexmedetomidine in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.	Dexmedetomidine is not registered for pediatric use.
		5.2 PopPK analysis of 4 studies (see: FDA “Pediatric Submission” (Ref. 1g), found the following estimates:	<u>Proposal:</u> Include the following indications for pediatric use in monograph: 1) premedication or (procedural) sedation 2) prevention of postoperative side effects

Source	Evidence	Effect	Remarks																								
Ref. 1g FDA Clinical Pharmacology Review: Pediatric Submission (dec 2012) NDA: 21-038 S21 S22 (FDA-Clinical_Pharmacology_Review)	Pharmacometrics review of pediatric PK studies	Clinical Pharmacology Findings PopPK analysis of four PK studies found the following PK parameter estimates:	One of four included PK studies can be identified as (Chrysostomou et al. 2014): Ref. 2b																								
		<table><tr><td></td><td colspan="2">geometric mean (95% CI)</td></tr><tr><td>Age</td><td>CL (L/h/kg)</td><td>Vd (L/kg)</td></tr><tr><td><1 month (n=28)</td><td>0.93 (0.76, 1.14)</td><td>0.83 (0.72, 0.95)</td></tr><tr><td>1 to <6 months (n=14)</td><td>1.21 (0.99, 1.48)</td><td>0.76 (0.57, 1.00)</td></tr><tr><td>6 to <12 months (n=15)</td><td>1.11 (0.94, 1.31)</td><td>0.99 (0.75, 1.31)</td></tr><tr><td>12 to <24 months (n=13)</td><td>1.06 (0.87, 1.29)</td><td>0.72 (0.55, 0.95)</td></tr><tr><td>2 to <6 years (n=26)</td><td>1.11 (1.00, 1.23)</td><td>0.96 (0.76, 1.21)</td></tr><tr><td>6 to <17 years (n=28)</td><td>0.80 (0.69, 0.92)</td><td>0.80 (0.61, 1.04)</td></tr></table>		geometric mean (95% CI)		Age	CL (L/h/kg)	Vd (L/kg)	<1 month (n=28)	0.93 (0.76, 1.14)	0.83 (0.72, 0.95)	1 to <6 months (n=14)	1.21 (0.99, 1.48)	0.76 (0.57, 1.00)	6 to <12 months (n=15)	1.11 (0.94, 1.31)	0.99 (0.75, 1.31)	12 to <24 months (n=13)	1.06 (0.87, 1.29)	0.72 (0.55, 0.95)	2 to <6 years (n=26)	1.11 (1.00, 1.23)	0.96 (0.76, 1.21)	6 to <17 years (n=28)	0.80 (0.69, 0.92)	0.80 (0.61, 1.04)	The other data come from studies by the MAH, result published on clinicaltrials.gov
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Lower weight-adjusted CL observed in neonates compared to infants.	Dosing used to determine C _{ss} is relatively high.																										
Observed average dose-normalized steady-state plasma concentrations upon 1 µg/kg over 10 min followed by 0.7 µg/kg/h (based on two PK studies):	<u>Proposal:</u> Include PK data (CL and Vd) to monograph and add to references.																										
<table><tr><td>Age</td><td>C_{ss} (pg/mL)</td></tr><tr><td>1 to <6 months</td><td>606</td></tr><tr><td>6 to <12 months</td><td>719</td></tr><tr><td>12 to 24 months</td><td>696</td></tr><tr><td>2 to <6 years</td><td>789</td></tr><tr><td>≥6 to 17 years</td><td>1203</td></tr><tr><td>adult (from label)</td><td>1370</td></tr></table>	Age	C _{ss} (pg/mL)	1 to <6 months	606	6 to <12 months	719	12 to 24 months	696	2 to <6 years	789	≥6 to 17 years	1203	adult (from label)	1370													
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Dose corresponds to dose for adults (“Precedex” label: loading dose of 1 µg/kg followed by maintenance dose of 0.2 - 0.7 µg/kg/h). Results of PopPK analyses with respect to the effect of cardiopulmonary bypass on dexmedetomidine PK are inconclusive. Dexmedetomidine is effective for sedation, although meta-analysis cannot be performed because studies used different sedation scales. A dose-effect relationship could not be determined because of confounding (midazolam treatment). Hypotensive and bradycardic effects were shown to be dose-dependent.																											
In adults, the main PK parameter values (CL, t _{1/2} and Vd) were consistent across several studies with varied infusion regimens.																											

2. Pharmacokinetic data

- Plasma protein binding: 94% (IM).
- Metabolism: predominantly N-glucuronidation, also N-methylation and oxidation by CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19 (IM).
- Excretion: approx. 95% via urine, approx. 4% via faeces. Less than 1% excreted unchanged via urine (IM).

Evidence	Effect	Remarks																																											
Ref. 2a PopPK study, n=95 (Evidence: B)	Dexmedetomidine pharmacokinetics in pediatric intensive care -a pooled analysis (Potts et al. 2009)	Indication: Sedation on the ICU Age:1 week - 14 years (mean 3.8 and median 3 years) Dosage: LD 1 - 6 µg/kg with/without MD 0.2 µg/kg/h Administration: IV Duration: LD 5 min (1 study) or 10 min (2 studies) or LD followed by MD 8 - 24h (1 study) (mean: 18.8h and median: 19.6h) <u>Proposal:</u> Include in PK section that CL may be lower in children who underwent cardiac surgery.																																											
	<u>Summary</u> PopPK analysis of four PK studies, with a two-compartment model, found the following population parameter estimates:																																												
	<table><tr><td></td><td>mean (CV%) or mean ±SD</td></tr><tr><td>CL (L/h/70kg)</td><td>42.1 (30.9%)</td></tr><tr><td>Central Vd (L/70kg)</td><td>56.3 (61.3%)</td></tr><tr><td>Peripheral Vd (L/70kg)</td><td>69.0 (47.0%)</td></tr><tr><td>Cmax (pg/mL)</td><td>670 ± 128 ^b</td></tr></table>			mean (CV%) or mean ±SD	CL (L/h/70kg)	42.1 (30.9%)	Central Vd (L/70kg)	56.3 (61.3%)	Peripheral Vd (L/70kg)	69.0 (47.0%)	Cmax (pg/mL)	670 ± 128 ^b																																	
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	Mean age-related CL predictions:																																												
	<table><tr><td>Age</td><td>CL (L/h/kg)</td></tr><tr><td>0</td><td>0.55</td></tr><tr><td>1 month</td><td>0.59</td></tr><tr><td>3 months</td><td>0.67</td></tr><tr><td>6 months</td><td>0.77</td></tr><tr><td>1 year</td><td>0.84</td></tr><tr><td>2 years</td><td>0.89</td></tr><tr><td>3 years</td><td>0.88</td></tr><tr><td>4 years</td><td>0.86</td></tr><tr><td>8 years</td><td>0.78</td></tr><tr><td>12 years</td><td>0.70</td></tr></table>		Age	CL (L/h/kg)	0	0.55	1 month	0.59	3 months	0.67	6 months	0.77	1 year	0.84	2 years	0.89	3 years	0.88	4 years	0.86	8 years	0.78	12 years	0.70																					
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Suggested dosage regimens to achieve target concentration of 0.6 µg/L at different ages:																																													
<table><tr><td>Age</td><td>Weight (kg)</td><td>LD (µg/kg), over 10 min (=2.9 µg/kg/h)</td><td>MD (µg/kg/h), general sedation</td><td>MD (µg/kg/h), postoperative cardiac infusion</td></tr><tr><td>neonate</td><td>3.5</td><td>0.6</td><td>0.33</td><td>0.24</td></tr><tr><td>3 months</td><td>6</td><td>0.6</td><td>0.40</td><td>0.29</td></tr><tr><td>6 months</td><td>7.5</td><td>0.6</td><td>0.46</td><td>0.34</td></tr><tr><td>1 year</td><td>10</td><td>0.6</td><td>0.51</td><td>0.37</td></tr><tr><td>2 years</td><td>12</td><td>0.6</td><td>0.53</td><td>0.39</td></tr><tr><td>5 years</td><td>20</td><td>0.6</td><td>0.49</td><td>0.36</td></tr><tr><td>8 years</td><td>25</td><td>0.6</td><td>0.47</td><td>0.34</td></tr><tr><td>20 years</td><td>70</td><td>0.6</td><td>0.36</td><td>0.26</td></tr></table>	Age	Weight (kg)	LD (µg/kg), over 10 min (=2.9 µg/kg/h)	MD (µg/kg/h), general sedation	MD (µg/kg/h), postoperative cardiac infusion	neonate	3.5	0.6	0.33	0.24	3 months	6	0.6	0.40	0.29	6 months	7.5	0.6	0.46	0.34	1 year	10	0.6	0.51	0.37	2 years	12	0.6	0.53	0.39	5 years	20	0.6	0.49	0.36	8 years	25	0.6	0.47	0.34	20 years	70	0.6	0.36	0.26
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Immature clearance in the first year of life and a higher CL (in L/h/kg) in small children dictate infusion rates that change with age. Extrapolation of dose from children given infusion in intensive care after cardiac surgery may not be applicable to those sedated for noninvasive procedures out of intensive care as children receiving dexmedetomidine infusion after cardiac surgery had a reduced CL of 27% compared to a population given bolus dose (though CL in these children given bolus immediately after surgery was similar to the rest of the population). Simulation of published infusion rates that provide adequate sedation for intensive care patients found a target therapeutic concentration of between 400 and 800 pg/mL (similar sedation target as adults).																																													

Evidence	Effect	Remarks															
Ref. 2b Prospective study n=42 (Evidence: C)	A Phase II/III, Multicenter, Safety, Efficacy, and Pharmacokinetic Study of Dexmedetomidine in Preterm and Term Neonates (Chrysostomou et al. 2014) <u>Summary</u> Non-compartmental analysis of a dose-escalation study (3 levels) found the following estimates of PK parameters (median with range): <table><tr><th></th><th>preterm neonates GA 28-35 weeks</th><th>full-term neonates GA 36-44 weeks</th></tr><tr><td>Cmax (pg/mL)</td><td>102 (34 - 505)</td><td>192 (56 - 1394)</td></tr><tr><td>Vd (L/kg)</td><td>2.7 (2.5 - 5.9)</td><td>3.9 (0.1 - 10.9)</td></tr><tr><td>CL (L/kg/h)</td><td>0.3 (0.2 - 0.4)</td><td>0.9 (0.2 - 1.5)</td></tr><tr><td>t1/2 (h)</td><td>7.6 (3.0 - 9.1)</td><td>3.2 (1.0 - 9.4)</td></tr></table> Differences between preterm and full-term neonates were not statistically different. The PK profile of dexmedetomidine appears to be different in neonates compared with older children and adults. Preterm neonates and, to a lesser extent, term neonates had larger Vd, increased free unbound dexmed, decreased CL, increased t1/2, and significantly increased AUC. This indicates that lower doses may be required to achieve the same level of sedation and to avoid adverse effects. Dexmed is effective for sedating critically ill, initially intubated and mechanically ventilated preterm and full-term neonates and is well-tolerated without significant AEs.		preterm neonates GA 28-35 weeks	full-term neonates GA 36-44 weeks	Cmax (pg/mL)	102 (34 - 505)	192 (56 - 1394)	Vd (L/kg)	2.7 (2.5 - 5.9)	3.9 (0.1 - 10.9)	CL (L/kg/h)	0.3 (0.2 - 0.4)	0.9 (0.2 - 1.5)	t1/2 (h)	7.6 (3.0 - 9.1)	3.2 (1.0 - 9.4)	Indication: Mechanical ventilation (sedation in the ICU) Age: GA ≥28 to ≤44 weeks Weight: 2.6 ± 1.0 kg (mean ± SD) Dosage: LD (µg/kg) + MD (µg/kg/h) of 0.05 + 0.05 or 0.1 + 0.1 or 0.2 + 0.2 Administration: IV Duration: LD in 10-20 min, MD 6 - 24 hours Relatively low dose, at the lower end of being effective? <u>Proposal:</u> -
	preterm neonates GA 28-35 weeks	full-term neonates GA 36-44 weeks															
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t1/2 (h)	7.6 (3.0 - 9.1)	3.2 (1.0 - 9.4)															
Ref. 2c PopPK study, n=59 (Evidence: B)	Dexmedetomidine Pharmacology in Neonates and Infants After Open Heart Surgery (Su et al. 2016) <u>Summary</u> PopPK analysis of a dose-escalation study (3 dose levels), with a two-compartment model, found the following estimates: <table><tr><th></th><th>typical full term *</th><th>2 weeks</th><th>1 month</th></tr><tr><td>CL (mL/min/kg)</td><td>10</td><td>18.2</td><td>18.4</td></tr></table> <i>*typical full-term newborn, median weight (3.4 kg) without right-to-left intracardiac shunting, and with a median bypass time of 60 min postoperative from cardiac surgery</i> Cohort of neonates (<1 month) and cohort of infants (1-24 months), 3 dosing groups per cohort. Only PK parameters for neonates are provided. Based on the simulations, time to steady-state (380 - 450 pg/mL) is approximately 6h after the initiation of a LD of 0.5 µg/kg followed by a MD of 0.4 µg/kg/h for a typical infant. Neonates achieve higher plasma concentrations (>600 pg/mL) with longer times to steady-state (>10 h) when administered equivalent µg/kg doses. Dexmedetomidine CL is significantly diminished in full-term newborns and increases rapidly in the first few weeks of life (until approx.1 month). Therefore, neonates require an approx. 30% to 40% reduction in weight-based dose (µg/kg) to achieve similar C _{ss} when compared with infants. Dexmedetomidine PK may be influenced by age during the neonatal period, weight, total bypass time, and intracardiac shunting. Dose-limiting toxicity occurred in neonates, maximum tolerable dose (MTD) was exceeded at 0.4 µg/kg/h. Continuous infusions of up to 0.3 µg/kg/h in neonates and 0.75 µg/kg/h in infants were well tolerated after open heart surgery.		typical full term *	2 weeks	1 month	CL (mL/min/kg)	10	18.2	18.4	Indication: Mechanical ventilation after open heart surgery (sedation in the ICU) Age: 1 day - 20.4 months, median 4.3 months Dosage: LD (µg/kg) + MD (µg/kg/h), infants: 0.35 + 0.25 or 0.7 + 0.5 or 1 + 0.75; neonates: 0.25 + 0.2 or 0.35 + 0.3 or 0.5 + 0.4 Administration: IV Duration: 10.1 (3.2 - 24.3) h, median (range) <u>Proposal:</u> -							
	typical full term *	2 weeks	1 month														
CL (mL/min/kg)	10	18.2	18.4														

Evidence	Effect	Remarks																				
Ref. 2d PopPK study, n=20, 89 samples (Evidence: B)	Population Pharmacokinetics of Dexmedetomidine in Infants (Greenberg et al. 2017) <u>Summary</u> PopPK analysis with a one-compartment model, found the following estimates (median or range): <table><tr><td>Cmax (pg/mL)</td><td>680 - 1420</td></tr><tr><td>CL (L/h/kg)</td><td>0.87 - 2.65</td></tr><tr><td>Vd (L/kg)</td><td>1.5</td></tr></table> Of the 20 infants, 3 were born prematurely at a GA of 27, 32, and 32 weeks (PMA at time of first PK sampling was 40, 32, and 61 weeks, resp.). Most (16/20) children were on mechanical ventilation. First to study dexmedetomidine PK in infants at doses >0.2 µg/kg/h and in any child >0.75 µg/kg/h. The median maximum dose received by participants in the current study (1.8 µg/kg/h) was 9-times and 2.4-times greater than the maximum dose studied previously in infants and in older children, resp. No association between dexmedetomidine exposure and adverse events was found. CL in infants was greater than reported in neonates but lower than that in adults. Vd in infants was comparable to reports in children and adults. Infants with younger PMA and recent cardiac surgery may require relatively lower dose to achieve exposure similar to older patients and those without cardiac surgery.	Cmax (pg/mL)	680 - 1420	CL (L/h/kg)	0.87 - 2.65	Vd (L/kg)	1.5	Indication: Analgesia or sedation (not specified) in the ICU Age: PNA: 4 - 203 days, median 43 days, GA 27-40 weeks, median 39 weeks Dosage: LD of 0.1 - 3 (median 0.5) µg/kg and MD of 0.1 - 2.5 (median 1) µg/kg/h Administration: IV Duration: not specified <u>Proposal:</u> Include in PK section that CL may be lower in children who underwent cardiac surgery.														
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CL (L/h/kg)	0.87 - 2.65																					
Vd (L/kg)	1.5																					
Ref. 2e PopPK study, n=18, 148 samples (Evidence: B)	Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study (Miller et al. 2018) <u>Summary</u> Estimates of Cmax and Tmax were found by non-compartmental analysis and a two-compartment PopPK analysis was conducted to estimate Vd and CL, median (range): <table><tr><td></td><td>Intranasal 1 µg/kg</td><td>Intranasal 2 µg/kg</td><td>IV 1 µg/kg</td></tr><tr><td>Cmax (pg/mL)</td><td>182 (163 - 251)</td><td>324 (229 - 597)</td><td>783 (460 - 1030)</td></tr><tr><td>Tmax (min)</td><td>46.5 (31 - 62)</td><td>45.5 (32 - 65)</td><td>-</td></tr><tr><td>Vd (L)</td><td>11.3 (6.8 - 14.0)</td><td>11.4 (3.4 - 17.8)</td><td>8.51 (6.78 - 13.3)</td></tr><tr><td>CL (L/min)</td><td>0.246 (0.192 - 0.342)</td><td>0.285 (0.243 - 0.326)</td><td>0.301 (0.223-0.367)</td></tr></table> Atomised intranasal administration of 1 µg/kg resulted in a plasma concentration of approx. 100 pg/mL (low end reported for sedative efficacy) within 20 min (peak: 199 pg/mL in 46 min) while this concentration is reached within 10 min with a dose of 2 µg/kg (also: approx. 2-times higher Cmax). The typical bioavailability was estimated as 83.8% with a 95% CI of 69.5-98.1% and 8.72% RSE.		Intranasal 1 µg/kg	Intranasal 2 µg/kg	IV 1 µg/kg	Cmax (pg/mL)	182 (163 - 251)	324 (229 - 597)	783 (460 - 1030)	Tmax (min)	46.5 (31 - 62)	45.5 (32 - 65)	-	Vd (L)	11.3 (6.8 - 14.0)	11.4 (3.4 - 17.8)	8.51 (6.78 - 13.3)	CL (L/min)	0.246 (0.192 - 0.342)	0.285 (0.243 - 0.326)	0.301 (0.223-0.367)	Indication: sedation after elective cardiac surgery Age: 6-44 months Dosage: 1 or 2 µg/kg Administration: intranasal or IV Duration: intranasal: single dose; IV: 10 min <u>Proposal:</u> Supports intranasal dosing recommendation.
	Intranasal 1 µg/kg	Intranasal 2 µg/kg	IV 1 µg/kg																			
Cmax (pg/mL)	182 (163 - 251)	324 (229 - 597)	783 (460 - 1030)																			
Tmax (min)	46.5 (31 - 62)	45.5 (32 - 65)	-																			
Vd (L)	11.3 (6.8 - 14.0)	11.4 (3.4 - 17.8)	8.51 (6.78 - 13.3)																			
CL (L/min)	0.246 (0.192 - 0.342)	0.285 (0.243 - 0.326)	0.301 (0.223-0.367)																			

Evidence	Effect	Remarks								
Ref. 2f PopPK study, n=6 (Evidence: A2)	Dose rationale and pharmacokinetics of dexmedetomidine in mechanically ventilated newborns: impact of design optimization (van Dijkman et al. 2019) <u>Summary</u> The following estimate of CL for a typical neonate (PMA 40 weeks, 3.4 kg) was found using PopPK analysis: CL = 2.92 L/h (mean). A published PopPK model* was used to derive dosing regimen for a first-in-neonate study and the optimised schedule was implemented in a neonatal pilot study (n=6). Simulations shows a 20% higher CL compared to initial estimates obtained by extrapolation from a slightly older pediatric population. Extension with 11 additional subjects showed a further increased CL in preterm subjects with lower PMA. Therefore, dose was increased to 0.4 µg/kg/h in the follow-up phase of this trial.	Indication: analgo-sedation in mechanical ventilation Age: GA: 34 - 40 weeks, PNA: 0 - 23 days Birth weight: 1.9 - 4.3 kg Dosage: 0.3 µg/kg/h Administration: IV Duration: 24h * Potts et al. 2009 Conclusion (“higher CL at younger PMA”) not in line with findings of other studies. <u>Proposal:</u> -								
Ref. 2g Open cohort study, n=7, 94 samples (Evidence: B)	Dexmedetomidine Pharmacokinetics in Neonates with Hypoxic-Ischemic Encephalopathy Receiving Hypothermia (McAdams et al. 2020) <u>Summary</u> Non-compartmental analysis found the following PK parameters (range with (mean ± SD)): <table><tr><td>Cmax (pg/mL)</td><td>295 - 929 (537 ± 180)</td></tr><tr><td>Tmax (h)*</td><td>0.2 - 48.3 (31.0 ± 16.8)</td></tr><tr><td>CL (L/h/kg)</td><td>0.480 - 0.968 (0.761 ± 0.155)</td></tr><tr><td>Vd (L/kg)</td><td>1.95 - 8.88 (5.22 ± 2.62)</td></tr></table> *Tmax 0.2h was an outlier, the other 6 ranged from 24.0 to 48.3h Population estimates of CL and Vd for the 1-compartment model, 0.697 L/h/kg and 7.48 L/kg, resp., are also reasonably consistent with estimates derived from non-compartmental analysis. GA, PMA, body weight, max. serum creatinine and serum ALT don't appear to significantly influence dexmedetomidine PK. CL was either comparable or lower and Vd was larger in cooled newborns with HIE compared to corresponding estimates previously reported* for uncooled normothermic newborns without HIE. As a result, plasma concentrations in cooled newborns with HIE rose more slowly in the initial hours of infusion compared to predicted concentration-time profiles based on reported PK parameters in normothermic newborns without HIE, while similar steady-state levels were achieved. No acute adverse events were associated with dexmed. A loading dose or more rapid escalation in initial titration of infusion may be needed to overcome the initial lag in rise of plasma concentration.	Cmax (pg/mL)	295 - 929 (537 ± 180)	Tmax (h)*	0.2 - 48.3 (31.0 ± 16.8)	CL (L/h/kg)	0.480 - 0.968 (0.761 ± 0.155)	Vd (L/kg)	1.95 - 8.88 (5.22 ± 2.62)	Indication: moderate to severe HIE (undergoing hypothermia) Age: PNA 1.7 ± 0.5 days, GA 37+3 to 41+5 weeks+days (mean ± SD: 39.6 ± 1.4 weeks) Birth weight: 3501 ± 588 g (mean ± SD) Dosage: start 0.2, increased after 1h to 0.3 and after another 2.5h to 0.4 µg/kg/h Administration: IV Duration: 54.3 - 74h (mean ± SD: 64.8 ± 6.9h) * Compared to data from (Chrysostomou et al. 2014, Greenberg et al. 2017, Potts et al. 2009) <u>Proposal:</u> Include in PK section that PK may be altered (reduced CL and increased Vd) in case of therapeutic hypothermia and that a loading dose or more rapid escalation may be required.
Cmax (pg/mL)	295 - 929 (537 ± 180)									
Tmax (h)*	0.2 - 48.3 (31.0 ± 16.8)									
CL (L/h/kg)	0.480 - 0.968 (0.761 ± 0.155)									
Vd (L/kg)	1.95 - 8.88 (5.22 ± 2.62)									

AE = adverse event, ALT = alanine transaminase, AUC = area under the plasma concentration-time curve, CL = clearance, Cmax = maximum plasma concentration, CV% = coefficient of variation, GA = gestational age, HIE = hypoxic-ischemic encephalopathy, ICU = intensive care unit, LD = loading dose, MD = maintenance dose, PK = pharmacokinetic, PopPK = population pharmacokinetic, PMA = postmenstrual age, RSE = relative standard error, t1/2 = half-life, Tmax = time to maximum plasma concentration, Vd = volume of distribution.

3. Efficacy data on use as Premedication

Evidence	Effect	Remarks
Ref. 3a Meta-analysis, n=13 RCTs 531 patients (Evidence: A1)	Dexmedetomidine vs midazolam as preanesthetic medication in children: a meta-analysis of randomized controlled trials (Pasin et al. 2015) <u>Summary</u> In the dexmedetomidine group there was a higher incidence of satisfactory sedation at separation from parents (RR 1.30, 95% CI 1.05-1.62), a reduced incidence of postoperative agitation (RR 0.31, 95% CI 0.13-0.73) and a significant reduction in the rescue doses of analgesic drugs (RR 0.52, 95% CI 0.39-0.70). There was no evidence of a higher incidence of satisfactory sedation at anesthesia induction or any reduction of duration of surgery and anesthesia. Most (8/9) intranasal studies used a dose of 1 µg/kg (of which one study also had a group receiving 0.5 µg/kg).	Indication: premedication for induction of anesthesia Age: not specified Dosage: 0.5 - 4 µg/kg Administration (n=number of studies): intranasal (n=9), oral (n=2), or sublingual (n=1) Duration: single dose Did not include systematic reviews/meta-analyses of Peng et al. 2014 and Sun et al. 2014 in RA file because of overlap of included studies (11/13 studies included by Peng et al. and 12/13 studies included by Sun et al.) <u>Proposal</u> -
Ref. 3b Meta-analysis, n=12 RCTs, 454 patients (Evidence: A1)	Effects of dexmedetomidine versus midazolam for premedication in paediatric anaesthesia with sevoflurane: A meta-analysis (Feng et al. 2017) <u>Summary</u> Patients receiving dexmedetomidine had a lower incidence of unsatisfactory sedation (RR 0.71, 95% CI 0.57-0.89), unsatisfactory parental separation (RR 0.56, 95% CI 0.35-0.87) and rescue analgesics (RR 0.52, 95% CI 0.35-0.77) than patients in midazolam group. Incidence of unsatisfactory mask acceptance, EA and PONV was similar. Intranasal doses used: 1 - 1.5 µg/kg (1 study: 0.6 µg/kg/h intranasal). Most (4/5) intranasal studies also included by Pasin et al. 2015 (ref. 3a)	Indication: premedication for induction of anesthesia Age: 1 - 12 years Dosage: 0.5 - 4 µg/kg or 0.6 µg/kg/h (n=1 study) Administration (n=number of studies): intranasal (n=5) or oral (n=7) Duration: single dose or continuous infusion <24h (n=1 study) <u>Proposal</u> -

Evidence	Effect	Remarks
Ref. 3c Systematic review and meta-analysis, n=13 RCTs, 626 patients (Evidence: A1)	The effects of intranasal dexmedetomidine premedication in children: a systematic review and meta-analysis (Jun et al. 2017) <u>Summary</u> Intranasal dexmedetomidine premedication provided more satisfactory sedation at parent separation (RR 1.45, 95% CI 1.19-1.76) than other premedication regimens. Dexmedetomidine also reduced the need for rescue analgesics (RR 0.58, 95% CI 0.40-0.83), was associated with a lower incidence of nasal irritation (RR 0.05, 95% CI 0.01-0.36) and PONV (RR 0.63, 95% CI (0.40-0.99) and a lower systolic blood pressure (weighted mean difference -6.7 mmHg, 95% CI -10.5 to -2.9) and heart rate (weighted mean difference -6.8 beats/min, 95% CI -11.3 to -2.6) No difference in sedation at mask induction or incidence of ED were seen between dexmedetomidine and other premedication treatments. Most (11/13) studies used a dose of 1 µg/kg. Most (8/11) studies also included by Pasin et al. 2015, Ref. 3a.	Indication: premedication for induction of anesthesia Age: 2.7 - 9.5 years (medians or means of studies) Dosage: 0.5 - 2 µg/kg Administration: intranasal Duration: single dose <u>Proposal</u> Basis for intranasal dose for premedication.
Ref. 3d Systematic review and meta-analysis, n=15 RCTs, 1316 patients (Evidence: A1)	Comparison of dexmedetomidine with chloral hydrate as sedatives for pediatric patients: A systematic review and meta-analysis (Lian et al. 2020) <u>Summary</u> Compared with CH, the dexmedetomidine group had a higher success rate of sedation (RR 1.14, 95% CI 1.05-1.25), however subgroup analysis revealed that only the 2 µg/kg dexmedetomidine dose group differed significantly from the CH group with respect to the success rate of sedation (no difference between CH vs. 1 / 1.5 / 2.5 / 3 µg/kg dexmed). There was no significant difference in the number of subjects who required 2 doses or the duration of sedation between CH and dexmedetomidine groups. CH group had a longer sedation latency (mean difference [MD] -3.54, 95% CI -5.94 to -1.15), sedation recovery time (MD -30.08, 95% CI -46.77 to -13.39), total time from sedative administration to discharge (MD -12.73, 95% CI -15.48 to -9.97). Also, the higher number of total adverse events (RR 0.25, 95% CI 0.11-0.61) was higher in the CH group, more specifically: CH was associated with higher risks of vomiting (RR 0.07, 95% CI 0.03-0.17), crying or resisting (RR 0.22, 95% CI 0.07-0.71) and cough (RR 0.15, 95% CI 0.05-0.44). There was no significant difference in the risk of hypotension, supplemental oxygen, or respiratory events between CH and dexmed. However, dexmedetomidine was associated with a higher risk of bradycardia (RR 4.08, 95% CI 1.63-10.21).	Indication: sedation (before surgery or diagnostic procedures) Age: 3.3 - 47 months (range of study means) Dosage: 1 - 3 µg/kg Administration (n=number of studies): intranasal (n=13), IV (n=1), oral (n=1) Duration: single dose or continuous infusion <u>Proposal</u> Basis for intranasal dose for (procedural) sedation.

CH = chloral hydrate, CI = confidence interval, EA = emergence agitation, ED = emergence delirium, PONV = postoperative nausea and vomiting, RR = relative risk.

4. Efficacy data on use for Prevention of postoperative side effects

EA = emergence agitation, ED = emergence delirium, LD = loading dose, MD = maintenance dose

Evidence	Effect	Remarks
Ref. 4a Systematic review and meta-analysis, n=58 RCTs and 5 case control studies, total of 7714 patients (Evidence: A1)	The Effect of Dexmedetomidine on Emergence Agitation or Delirium in Children After Anesthesia-A Systematic Review and Meta-Analysis of Clinical Studies (Rao et al. 2020) <u>Summary</u> Dexmedetomidine significantly decreased the incidence of post-anesthesia EA or ED compared with placebo (OR 0.22, 95% CI 0.16-0.32), midazolam (OR 0.36, 95% CI 0.21-0.63) and opioids (OR 0.55, 95% CI 0.33-0.91). Dexmedetomidine did not exhibit significant superiority compared with propofol, ketamine, clonidine, chloralhydrate, melatonin, and ketofol.	Indication: prevention of EA or ED following anesthesia Age: 0 months - 18 years Dosage: LD IV: 0.15 - 2.5 µg/kg, MD IV: 0.1 - 2 µg/kg/h, single intranasal dose: 1 - 2 µg/kg, single oral dose: 1 - 4 µg/kg Administration (n=number of studies): IV (n=39), intranasal (n=12), oral (n=5), caudal or nerve block (n=5), inhalation (n=1), transmucosal (n=1) Duration: single bolus (over 5 min) to maintenance dose (until the end of surgery) <u>Proposal</u> Basis for prevention of postoperative EA or ED, IV or intranasal administration.

EA = emergence agitation, ED = emergence delirium, LD = loading dose, MD = maintenance dose, OR = odds ratio.

Table 2 and 3 (below) provide an overview of the characteristics of studies (specified for route of administration) included and considered to be of "high quality" by Rao et al. 2020 (Ref 4a). An schematic overview of the different dosing regimens is shown in Figure 1.

Table 2. High quality studies (n=7) of Rao et al. (Ref. 4a) on IV dexmedetomidine use for prevention of postoperative side effects

Study	n	Age	Dose	Duration	Conclusion	Remarks
(Chen et al. 2013)	27	4.1 ± 1.3 yrs (mean ± SD)	LD 1 µg /kg in 1 min + MD 1 µg/kg/h after induction	35.8 (7.3) min, mean (SD)	Dexmedetomidine and ketamine prevent POA and pain after strabismus surgery. Dexmedetomidine also prevents POV.	Selected 1 µg/kg as previous studies showed unsatisfactory level of sedation for ophthalmic surgery with 0.7 µg/kg.
(Cho et al. 2020)	34	2-12 yrs 6.7 ± 2.4 (mean ± SD)	Bolus 0.3 µg/kg in 5 min, 5 min before end of surgery	single dose	Dexmedetomidine and midazolam prevent ED and dexmedetomidine showed statistically higher postoperative analgesic effect.	-
(Hauber et al. 2015)	195	6.1 ± 1.6 yrs (mean ± SD)	Rapid bolus 0.5 µg/kg, 5 min before the end of surgery	single dose	Dexmedetomidine improved recovery profile, less postoperative opioid use and a trend of fewer adverse events (compared to saline).	Dose-response studies suggest an effective dose range between 0.3 and 1.0 µg/kg.
(He et al. 2013)	61	4.6 ± 1.5 yrs (0.5 µg/kg) 4.7 ± 1.8 yrs (1 µg/kg) (mean ± SD)	Bolus 0.5 or 1.0 µg/kg in 10 minutes, after LMA insertion	single dose	Dexmedetomidine showed a dose-dependent decrease of sevoflurane required for LMA removal and less EA (compared to saline). Pain incidence was comparable. Between the dexmedetomidine dose groups, EA was comparable.	Dose selected because pilot study showed that 2 µg/kg resulted in kids that are sleepy and unresponsive for a long time after surgery, though 2 µg/kg were safe and effective for MRI procedures.
(Kim et al. 2014)	47	4.26 ± 1.36 yrs (mean ± SD)	Continuous infusion of 0.2 µg/kg/h, after induction to the end of surgery	26.14±8.03 min (mean ± SD)	Intra-operative low-dose dexmedetomidine in addition to fentanyl reduces EA.	Low dose (1/3 of recommended and without LD) but found to be sufficient for EA prevention (without compromising haemodynamics).
(Song et al. 2016)	78	2-6 years, 4.3 ± 1.7 yrs (0.25 µg/kg) 4.5 ± 1.3 yrs (0.5 µg/kg) 4.6 ± 1.3 yrs (1 µg/kg) (mean ± SD)	Bolus 0.25, 0.5, or 1.0 µg/kg in 10 min, at the start of the induction	single dose	Dexmedetomidine decreased EA without increasing intraoperative oculocardiac reflex (compared to saline).	1 µg/kg was more effective for EA than lower doses.
(Tsiotou et al. 2018)	31	3-14 years, 6.1 ± 2.6 yrs (mean ± SD)	Bolus 1 µg/kg in 10 min,after induction	single dose	Dexmedetomidine reduces the incidence and severity of ED without prolonging extubation time.	Lack of prolongation of extubation time probably due to only bolus dose. Optimal dose for opioid-sparing effect: ≥ 0.5 µg/kg.

EA = emergence agitation, ED = emergence delirium, LD = loading dose, LMA = laryngeal mask airway, MD = maintenance dose, POA = post-operative agitation, POV = post-operative vomiting

Table 3. High quality studies (n=5) of Rao et al. (Ref 4a) on intranasal dexmedetomidine use (single dose) for the prevention of postoperative side effects

Study	n	Age	Dose	Conclusion	Remarks
(Akin et al. 2012)	45	5 (3-9) years [median (IQR)]	1 µg/kg, 45-60 min before induction	Dexmedetomidine and midazolam decrease anxiety upon separation from parents. Midazolam is superior for mask induction.	Dose may be inadequate for facilitating face mask induction (also: Cmax not reached at time of face mask induction)
(Bi et al. 2019)	20	6-48 months, 17.2 ± 6.3 months (mean ± SD)	1 µg/kg, 25 min before induction	Dexmedetomidine reduced laryngospasm, breath-holding, and coughing (compared to saline) and it reduced POA without a prolonged recovery time.	2 µg/kg or higher significantly prolong recovery time
(Pestieau et al. 2011)	51	1.7 (0.9 - 4.2) years (1 µg/kg) 1.7 (0.7 - 6.9) years (2 µg/kg) [median (range)]	1 µg/kg or 2 µg/kg, after induction	Length of PACU stay was significantly longer in 2 µg/kg-treated compared with 1 µg/kg -treated, fentanyl-treated, or the control group (only acetaminophen was needed in the PACU).	Higher doses (2 µg/kg) might not have a role for analgesia in procedures of short duration. Possibly no prolongation of PACU stay when administered before induction / several min before surgical procedure.
(Yao et al. 2015)	60	4.5 ± 0.8 years (1 µg/kg) 4.4 ± 0.8 years (2 µg/kg) (mean ± SD)	1 µg/kg or 2 µg/kg, 45 min before induction	Dexmedetomidine dose-dependent reduction in the minimum alveolar concentration for LMA insertion and less ED without delaying PACU discharge, and improves parental satisfaction.	-
(Zhang et al. 2020)	67	3.0 (2-4) years [median (IQR)]	1.5 µg/kg, 30-45 min before induction	Reduction of peri-operative respiratory adverse events in children <3 yrs (compared to saline), not >3 yrs. No difference in EA, fever or vomiting (compared to saline).	Children >3 years may require a higher dose to achieve the same reduction in the incidence of respiratory events. Used previously for sedation before surgery and procedure examinations: 1.0, 1.5, 2.0 µg/kg or even higher.

Cmax = maximum plasma concentration, EA = emergence agitation, ED = emergence delirium, LMA = laryngeal mask airway, PACU = post-anesthesia care unit, POA = post-operative agitation

Source	Indication	Age	Dose
Miller et al. 2018	elective cardiac surgery (?)	6 - 44 months	1 or 2 µg/kg
Jun et al. 2017 SR/MA	Review for indication "premedication"	-	0.5 - 2 µg/kg
Lian et al. 2020 SR/MA	Review for indication "sedation"	-	1 - 3 µg/kg
Rao et al. 2020 SR/MA	Review for indication "prevention of postoperative side effects"	-	1 - 2 µg/kg
Suggested:	Premedication or (procedural) sedation Prevention of postoperative side effects	0 – 18 years (incl. neonates)	1 - 2 µg/kg

Table 4. Overview of the included studies on intranasal dexmedetomidine dosing. SR/MA = systematic review/meta-analysis.

Prevention of postoperative side effects

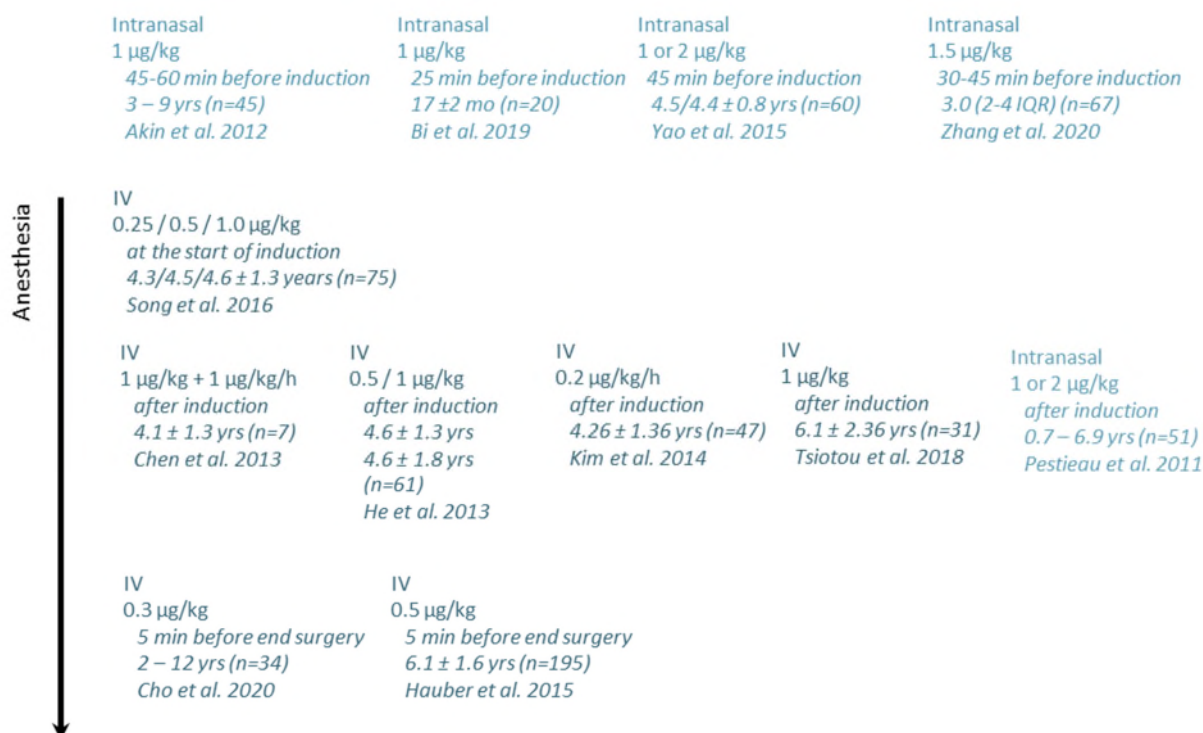


Figure 1. Overview of the various dosing regimens (intranasal and IV) of dexmedetomidine for the prevention of postoperative side effects (studies of Table 2 and 3, Rao et al. 2020).

5. Additional information

- **Renal function:** There is no information available for potential dose adjustments in case of impaired renal function.
- **Obesity:** With children with obesity, based on limited information, it is recommended to dose based on ideal body weight (IBW) (Ross et al. 2015). This can be calculated as follows: Ideal body weight (reflective of lean body mass in children (age 2–20)) = (50% BMI for age) x (height [m])².

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Online Resource 3 – Literature grading system

Level of evidence	Study on pharmacokinetics		Study on effect	
	0		0	
	Summary of Product Characteristics (SmPC)		Summary of Product Characteristics (SmPC)	
	A1		A1	
	Externally validated PopPK study		Systematic reviews or meta-analyses covering at least some A2-level studies	
	A2		A2	
	Internally validated PopPK study / PK multi-dose study		RCT of good quality and sufficient size	
	B		B	
	Non-validated PopPK study / PK single dose study		RCT of moderate quality or insufficient size or other comparative study (non-randomized, comparative cohort study, case-control study, retrospective study with sufficient patients and good controls)	
	C		C	
	Study with single PK parameter values (e.g. therapeutic drug monitoring data, single samples at steady-state)		Non-comparative study / Case reports / Case series / Retrospective study of moderate quality	

Individual studies included in the risk-benefit analysis document are graded according to their level of evidence. A different grading system is created for studies on pharmacokinetics compared to studies on effect. The level of evidence decreases from top to bottom (0 to C).