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Pharmacokinetics and Sedative Effects of Intranasal Dexmedetomidine in Ambulatory Pediatric Patients

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BACKGROUND: Our aim was to characterize the pharmacokinetics and sedative effects of intranasally (IN) administered dexmedetomidine used as an adjuvant in pediatric patients scheduled for magnetic resonance imaging (MRI) requiring sedation.

METHODS: This was an open-label, single-period study without randomization. Pediatric patients from 5 months to 11 years of age scheduled for MRI and receiving IN dexmedetomidine for premedication as part of their care were included in this clinical trial. Single doses of 2–3 $\mu g \cdot kg^{-1}$ of dexmedetomidine were applied IN approximately 1 hour before MRI. Five or 6 venous blood samples were collected over 4 hours for dexmedetomidine concentration analysis. Sedation was monitored with Comfort-B scores, and vital signs were recorded. Pharmacokinetic variables were calculated with noncompartmental methods and compared between 3 age groups (between 1 and 24 months, from 24 months to 6 years, and over 6–11 years).

RESULTS: We evaluated 187 consecutive patients for suitability, of which 132 were excluded. Remaining 55 patients were recruited, of which 5 were excluded before the analysis. Data from 50 patients were analyzed. The average (standard deviation [SD]) dose-corrected peak plasma concentration (C_{max}) was 0.011 $liter^{-1}$ (0.0051), and the median (interquartile range [IQR]) time to reach peak concentration (t_{max}) was 37 minutes (30–45 minutes). There was negative correlation with C_{max} versus age ($r = -0.58$; 95% confidence interval [CI], −0.74 to −0.37; $P < .001$), but not with t_{max} ($r = -0.14$; 95% CI, 0.14–0.39; $P = .35$). Dose-corrected areas under the concentration–time curve were negatively correlated with age ($r = -0.53$; 95% CI, 0.70 to −0.29; $P < .001$). Median (IQR) maximal reduction in Comfort-B sedation scores was 8 (6–9), which was achieved 45 minutes (40–48 minutes) after dosing. Median (IQR) decrease in heart rate was 15% (9%–23%) from the baseline.

CONCLUSIONS: Dexmedetomidine is relatively rapidly absorbed after IN administration and provides clinically meaningful but short-lasting sedation in pediatric patients. (Anesth Analg 2020;130:949–57)

KEY POINTS

- **Question:** What are the pharmacokinetics and sedative effects of intranasal dexmedetomidine in ambulatory sedation of children?
- **Findings:** Our results show that intranasal dexmedetomidine was quickly absorbed, its peak concentration achieved in a median time of 37 minutes, and the maximal sedative effect observed 45 minutes after dosing.
- **Meaning:** Our results demonstrate that intranasal 2–3 $\mu g \cdot kg^{-1}$ dexmedetomidine is absorbed relatively rapidly. Although clinically effective plasma concentrations are achieved, supplemental sedation seems to be required after a bolus dose to complete outpatient procedures.

The α-2 adrenoceptor agonist dexmedetomidine shows favorable characteristics as sedative agent, and several reports have been published describing its intravenous (IV) use for sedation of ambulatory pediatric patients[1,2] although there is no approval by Food and Drug Administration (FDA) or European Medicines Agency (EMA) for administration in the pediatric population.[3,4] Previous reports indicate that

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dexmedetomidine is safe and efficacious in children, but its sympatholytic properties and recovery profile especially after IV use may restrict its use in pediatric ambulatory care.[5]

Intranasal (IN) dosing represents a useful alternative dosing route for some drugs, especially in pediatric patients where IV access may not be available. Dexmedetomidine pharmacokinetics after IN dosing have not been studied in pediatric ambulatory patients; however, a recent report describes the pharmacokinetic profile after 1 or 2 $\mu g \cdot kg^{-1}$ IN dexmedetomidine dose for the first 2 hours in 12 pediatric patients undergoing heart surgery.[6] The onset for sedation in pediatric patients has been reported to occur 10–33 minutes after 2–3 $\mu g \cdot kg^{-1}$ doses.[7–10] To our knowledge, there are no previous published studies evaluating the sedative dexmedetomidine concentrations on pediatric patients, but in adults, dexmedetomidine plasma concentrations of 0.3–0.7 $ng \cdot milliliter^{-1}$ have been reported to provide significant sedation.[11–13]

The pharmacokinetics of dexmedetomidine are still poorly characterized in pediatric patients, and further studies are warranted.[6] Our main objective was to evaluate the absorption and pharmacokinetics of IN dexmedetomidine after 2–3 $\mu g \cdot kg^{-1}$ dose in pediatric patients scheduled for magnetic resonance imaging (MRI) requiring sedation. We also wanted to compare the pharmacological effects caused by singe IN dexmedetomidine to pharmacokinetics during pediatric sedation.

Our primary outcome was to determine the peak plasma concentrations (C_{max}) and time to C_{max} (t_{max}) after IN dexmedetomidine. We hypothesized that IN 2–3 $\mu g \cdot kg^{-1}$ dexmedetomidine leads to previously defined clinically effective plasma concentrations and coincide with the onset of action during MRI sedation in pediatric patients. Our secondary outcomes were area under time–concentration curve from 0 to 4 hours (AUC_{0-4h}) and the pharmacological effects caused by single IN dexmedetomidine to pharmacokinetics during pediatric sedation. We also evaluated the effect of age on dexmedetomidine pharmacokinetics and the effect our dosing regimen had on inducing clinically significant sedative effects in this patient population.

METHODS

This study was approved by the institutional review board (IRB) of the Hospital District of Southwest Finland (IRB number: 109/1800/2016). The trial was registered before patient enrollment at clinicaltrials.gov (NCT02955732; Principal investigator: P.U.; Date of registration: December 14, 2016) and in the EudraCT database (2016-002880-33; Principal investigator: P.U.; Date of registration: October 28, 2016). Written informed consent was obtained from the patients' legal guardians, and assent was obtained from all patients >6 years of age. This manuscript adheres to the applicable Transparent Reporting of Evaluations with Nonrandomized (TREND) guidelines.

Study Participants

Our aim was to recruit 50 pediatric patients with normal growth status (standard deviation [SD], –1.5; age-adjusted height between first and 99th percentiles of Finnish children), age between 1 month and 11 years of age, with guardians fluent in Finnish or Swedish (to understand the given information, to be able to give informed consent, and communicate with the study personnel), and scheduled to receive dexmedetomidine for sedation as part of their clinical care during MRI.

Patients with previous history of intolerance to the study drug or to related compounds and additives, previous drug therapy with dexmedetomidine in the 14 days before the study, use of stimulants or any drugs known to cause significant enzyme induction (eg, phenytoin), existing or recent significant disease that could influence the study outcome or cause a health hazard for the subject when participating in the study, clinically significant abnormal findings in physical examination or laboratory screening (routine hematology, renal function tests, and liver function tests [bilirubin]), or patients participating in any other clinical study involving investigational or marketed drug products concomitantly or within 1 month before the entry into this study were excluded.

Study Outline and Dexmedetomidine Administration

An open-label, exploratory study design was used. Patient recruitment and data collection were conducted at Turku University Hospital in Finland. Patients (and their guardians) potentially eligible for the study were approached for information, assessment of eligibility criteria, and consent either during a preceding clinic visit or on arrival in the hospital for the procedure. Venous blood samples and physiological data were collected from 50 pediatric patients who received dexmedetomidine for procedural sedation as part of their care.

Dexmedetomidine dosage used in this study (2–3 $\mu g \cdot kg^{-1}$) was based on previous reports[3,7,14] attesting to the safety of dexmedetomidine at doses up to 9 $\mu g \cdot kg^{-1}$ given IV over 30 minutes. The selection of the actual dose of dexmedetomidine used for each patient was determined by the anesthesiologist taking care of the patient, and it was based on the general condition of the patient and the anticipated need of required level of sedation. A dose of 2–3 $\mu g \cdot kg^{-1}$ of dexmedetomidine (dexmedetomidine hydrochloride 118 $\mu g \cdot milliliter^{-1}$, corresponding

to dexmedetomidine base 100 μg·milliliter^{-1}, Dexdor; Orion Pharma, Espoo, Finland) was administered IN using an LMA® MAD Nasal™ device (Teleflex MAD Nasal; Teleflex Inc, Research Triangle Park, NC) approximately 45–60 minutes before the scheduled MRI procedure to achieve sufficient sedative effect as discussed previously.[5,8] The individual dose was rounded to the nearest 10 μg. A volume of 0.5 mL per nares was considered to be the maximum volume, and larger volumes were divided between both nostrils. A suitable forearm vein was cannulated at this stage; its lumen was kept patent with a mandrin. Topical anesthetic cream (lidocaine 2.5% and prilocaine 2.5%, EMLA; AstraZeneca Inc, Södertälje, Sweden) was applied to some patients to facilitate cannulation. IV thiopental (thiopental sodium 25 mg·milliliter^{-1}, Pentocur; Abcur, Helsingborg, Sweden) 1–10 mg·kg^{-1} was given as rescue medication to supplement sedation, if required. If rescue medication was needed, effect parameters measured after the dosing were not analyzed. The decision to administer supplemental thiopental and the selection of the actual dose was made by the attending anesthesiologist.

Venous blood samples (1.0 mL each) were drawn into ethylenediaminetetraacetic acid (EDTA) tubes for drug analysis. Initial 2 samples were drawn during the assumed absorption phase, that is, 10 and 20 minutes after drug administration, 2 samples were drawn 30 and 45 minutes after drug administration, and finally 2 samples were drawn during the assumed elimination phase between 120 and 240 minutes. A 5-minute variance in sampling time was allowed for the first 3 samples, and a 10-minute variance was allowed in the sampling time of the fourth blood sample. Two remaining blood samples were collected between 120 and 240 minutes from drug administration to avoid blood sampling during MRI imaging. Plasma was separated within 30 minutes and stored at –70°C until analysis. Concentration analysis of dexmedetomidine in plasma is described in Supplemental Digital Content 1, Data, http://links.lww.com/AA/C843.

Pharmacokinetic Analysis

Actual sampling times were used for pharmacokinetic calculations. C_{max} and t_{max} were observed directly from the data. The area under the dexmedetomidine plasma concentration–time curve during 0–4 hours ($AUC_{0–4h}$) was estimated by means of the trapezoidal rule. We used the linear trapezoidal rule for increasing values and the logarithmic trapezoidal rule for decreasing concentrations. The apparent volume of distribution of dexmedetomidine was calculated during the early elimination phase (apparent volume of distribution [V_d·F^{-1}]) by the use of noncompartmental methods based on statistical moment theory. The pharmacokinetic analysis was performed with WinNonlin program (version 4.1; Pharsight Corp, Mountain View, CA).

Drug Effects

The psychomotor effects of IN dexmedetomidine were assessed by 2 pediatric anesthesiologists using the Comfort-B sedation scale (CBSS), which has been used to monitor sedation in procedural and intensive care sedation of pediatric patients. Sedation was assessed clinically acceptable if CBSS decreased ≥6 points.[15,16] Peripheral oxygen saturation (Spo_2) and heart rate (HR) were monitored continuously after drug administration. We analyzed the pharmacological effect parameters only until supplemental thiopental was administered to rule out the effects of thiopental.

Assessment of Local Tolerability and Safety

The local tolerability of IN dexmedetomidine was assessed and recorded real time by visual inspection (crying, nasal irritation, and running nose) by the investigator immediately during administration of IN dexmedetomidine and thereafter at 1, 2, 3, and 4 hours after dosing and at the end of the clinical observation period. We identified adverse events of special interest, including bradycardia, hypotension, and respiratory complications within 4 hours of dexmedetomidine administration. We defined bradycardia as a decrease in HR >30% of patient's median baseline HR or requiring intervention, including administration of atropine. We defined hypotension as decreased systolic or mean arterial blood pressure >30% from patient's median baseline blood pressure or requiring intervention, including administration of a fluid bolus, or initiation of vasopressor therapy. We defined respiratory complications as a drop of Spo_2 below 88% or apnoea. Adverse events were assessed real time and adjudicated by the primary investigator (P.U.) based on review of the patient's medical chart. Potential adverse events were reported immediately during the study.

Statistics and Sample Size

The C_{max} and t_{max} of IN dexmedetomidine were the primary outcome measures of the study, and all other pharmacokinetic parameters and pharmacological effects were secondary variables. The sample size was based on previous experience in similar pharmacokinetic studies.[17–19] To evaluate the difference between age groups and to account for a larger variability in absorption after IN dosing, we calculated that 14 patients were needed to demonstrate a 50% difference in the C_{max} between the age groups with a type I error of 5% and a statistical power of 80%. The data were evaluated for normality of distribution using probit plots and the Shapiro–Wilk *W*

Table 1. Clinical Characteristics of the Study Subjects, Grouped by Age

Parameter	All Patients (n = 50)	Age 0–2 y (n = 8)	Age 2–6 y (n = 24)	Age 6–11 y (n = 18)	*P* Value, Kruskal–Wallis Test
Age (y)	5.0 (2.4)	1.3 (0.53)	4.3 (0.95)	7.6 (1.32)	…
Weight (kg)	19.9 (6.9)	10.7 (1.2)	18.0 (3.2)	26.5 (5.7)	<.001
BMI (kg·m^{-2})	16.3 (2.2)	17.0 (3.3)	15.9 (1.6)	16.5 (2.2)	.49
Sex (F/M)	25/25	5/3	12/12	8/10	.70
Time from dose to MRI (min)	68 (45–88)	55 (33–71)	64 (34–87)	84 (64–99)	.07
MRI duration (min)	42 (35–53)	44 (36–65)	42 (30–50)	43 (34–55)	.74
Time from dose to discharge (h)	4.0 (3.8–4.4)	4.0 (3.7–4.4)	3.9 (3.7–4.3)	4.2 (3.9–4.8)	.32
Dexmedetomidine dose (µg·kg^{-1})	2.8 (0.34)	2.7 (0.35)	2.9 (0.33)	2.8 (0.33)	.45
Total thiopental dose (mg·kg^{-1})	2.4 (1.5–4.9)	4.5 (1.8–8.3)	2.6 (1.5–3.9)	1.8 (1.0–6.0)	.36
$T_{Dose,Thiopental}$ (min)	72 (53–95)	68 (39–96)	66 (50–96)	86 (69–96)	.35

Data are shown as mean ± standard deviation, except for times and total thiopental dose, which are given as median and interquartile range.
Abbreviations: BMI, body mass index; F, female; M, male, MRI, magnetic resonance imaging; $T_{Dose,Thiopental}$, time from dose to thiopental.

test. Concentrations were normalized to a 1 µg·kg^{-1} dose and log transformed before computing pharmacokinetic parameters for each individual, but nontransformed results are reported. The data were analyzed first as one group, after which the patients were allocated to 3 age groups to analyze the effect of age. The age groups were as follows: between 1 and 24 months of age (AG1), from 24 months to 6 years of age (AG2), and over 6–11 years of age (AG3). Maximal reductions in CBSS, HR, and Spo_2 readings were calculated before analysis. Pharmacokinetic parameters and pharmacological effects were compared with 1-way analysis of variance (ANOVA), while t_{max} and the other time parameters were compared with the Kruskal–Wallis test. Levene test for homogeneity of variances was used before ANOVA. The associations of dexmedetomidine concentrations in plasma and the pharmacokinetic parameters with pharmacological effects were evaluated using Pearson product moment correlation coefficient. The results are expressed as mean values and SD, except for categorical and time-related parameters that are reported as medians and interquartile range (IQR). The statistical significance level was set to $P < .05$. R software (version 3.4.2; www.r-project.org) and ggplot2 (version 2.2.1; ggplot2.tidyverse.org) were applied for statistical analysis and graphical presentations.

RESULTS

Patient Data

We evaluated 187 consecutive patients for suitability, of which 132 were excluded. A consent was obtained for 55 patients, who all were administered IN dexmedetomidine, but 5 patients were later excluded (Supplemental Digital Content 2, Figure 1, http://links.lww.com/AA/C844). In 1 case, general anesthesia was induced before MRI and the other 4 patients were excluded as adequate blood sampling could not be completed. Fifty patients were included in the final dataset and analyzed (age, 0.4–10.7 years; weight, 8.8–40.0 kg; Supplemental Digital Content 2, Figure 2, http://links.lww.com/AA/C844). Descriptors of the patient population and the 3 age groups are shown in Table 1.

Pharmacokinetics

The patient characteristics are presented in Table 1. IN dexmedetomidine dose of 3 µg·kg^{-1} was given to 43 patients, while 6 patients received 2 µg·kg^{-1} and 1 patient (3.17 years of age) received 3.7 µg·kg^{-1}. Dose-corrected dexmedetomidine concentrations are reported in Figure 1, and the calculated pharmacokinetic parameters are reported in Table 2. The individual plasma concentrations of dexmedetomidine are shown in Supplemental Digital Content 2, Figure 3, http://links.lww.com/AA/C844. The frequency (%) of t_{max} occurring at a particular sampling time window was 5 (10), 17 (34), 27 (54), and 1 (2) at 10, 20, 30, 45, and 60 minutes, respectively. There was negative correlation with C_{max} versus age ($r = -0.58$; 95% confidence interval [CI], −0.74 to −0.37; $P < .001$), but no evidence of association with t_{max} and age. Average (SD) AUC_{0-4h} was negatively correlated with age ($r = -0.53$; 95% CI, 0.70 to −0.29; $P < .001$). Sedative plasma concentrations of dexmedetomidine (ie, C_{max} >0.3 ng milliliter^{-1}) were achieved in 7, 22, and 17 patients in the 3 age categories, respectively.

Pharmacological Effects

The impact of IN dexmedetomidine administration on the pharmacological effect parameters is summarized in Figure 2 and Table 3. Decrease in CBSS was significantly correlated with C_{max} ($r = 0.34$; 95% CI, 0.067–0.56; $P < .016$), but not with t_{max}. The CBSS reductions were not significantly associated with age or dose of IN dexmedetomidine. Based on clinical judgment, almost all patients required additional sedation, and 47 patients were dosed with thiopental (Table 1).

Cardiorespiratory Effects

Dexmedetomidine decreased HR and the lowest HRs before administration of supplemental thiopental in

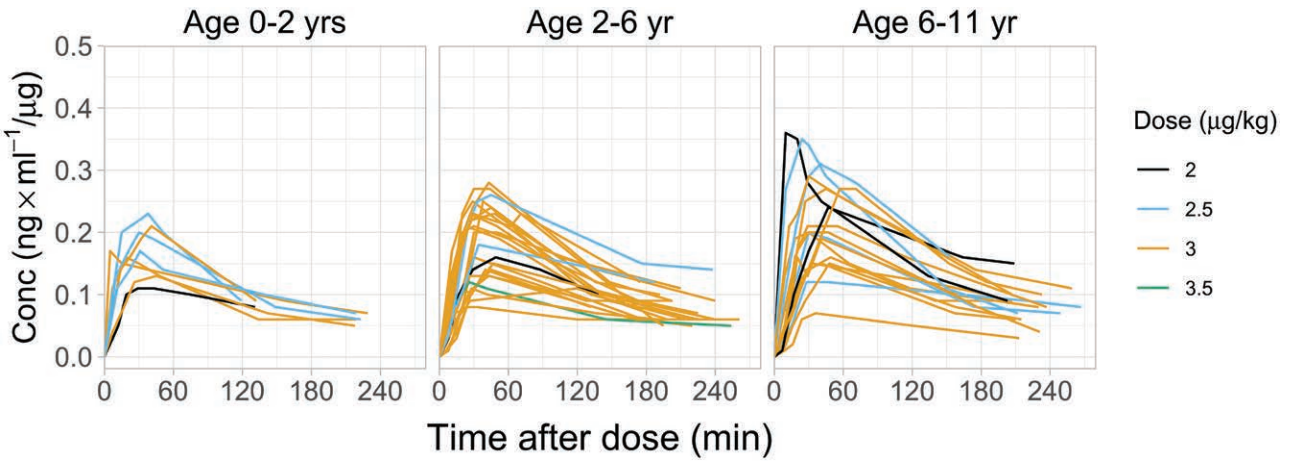

Figure 1. Dose-corrected dexmedetomidine concentrations in plasma after intranasal 2–3 µg·kg^{-1} dexmedetomidine dose as nasal spray in 50 ambulatory pediatric patients in the 3 age groups (0- to 2-y olds, 2- to 6-y olds, and 6- 11-y olds). Individual doses were rounded to the nearest 10 µg and shown as different dosing schemes highlighted with colors. Conc indicates concentration of dexmedetomidine in plasma.

Table 2. Pharmacokinetic Parameters of Dexmedetomidine After Administration of 2–3 µg·kg^{-2} Doses as Nasal Spray to 50 Ambulatory Paediatric Patients

Parameter	All Patients (n = 50)	Geometric Mean, 90% CI	Age 0–2 y (n = 8)	Age 2–6 y (n = 24)	Age 6–11 y (n = 18)	*P* Value, 1-Way ANOVA
C_{max} (ng·milliliter^{-1})	0.54 (0.17)	…	0.46 (0.11)	0.51 (0.17)	0.61 (0.18)	…
C_{max} D^{-1} (Liter^{-1})	0.011 (0.0051)	0.010 (0.0086–0.013)	0.016 (0.0048)	0.011 (0.0046)	0.0086 (0.0040)	<.001
t_{max} (min)	37 (30–45)	…	35 (22–43)	32 (28–45)	41 (30–47)	.52
AUC_{0-4} (ng·minute·liter^{-1})	68 (23)	…	61 (21)	69 (25)	77 (21)	…
AUC_{0-4} D^{-1} (minute·liter^{-1})	1.40 (0.61)	1.39 (1.15–1.60)	1.90 (0.51)	1.42 (0.66)	1.14 (0.45)	.0035
V_d F^{-1} (liter)	109 (56)	…	134 (68)	118 (58)	87 (45)	…
V_d F^{-1} D^{-1} (liter·µg^{-1})	1.98 (0.75)	1.98 (1.70–2.20)	2.28 (0.82)	1.97 (0.72)	1.85 (0.74)	.16

Abbreviations: CI, confidence interval; C_{max}, peak concentration in plasma; D, dexmedetomidine dose (µg); t_{max}, time to peak concentration; AUC_{0-4}, area under the plasma concentration–time curve from 0 to 4 h; V_d F^{-1}, apparent volume of distribution.

the 3 age groups 95 (11), 76 (13), and 69 (10) beats/min, respectively (Table 3; Figure 3). After dexmedetomidine, Spo_2 remained clinically acceptable (ie, >93%) in all patients. Immediately after the thiopental administration, 1 patient received supplemental oxygen due to decrease in Spo_2 to 91% (Figure 3).

Safety and Tolerability

IN dexmedetomidine was well tolerated. Nasal irritation was not observed in or reported by any of the patients, but crying was observed in 16 patients (32%) and runny nose in 8 patients (16%). One patient (5 years, 17 kg) received a single dose of atropine for bradycardia of 36 minute^{-1}, occurring soon after dosing of thiopental, 57 minutes after dexmedetomidine.

No serious adverse events related to study drug were reported. The reported adverse effects were mild and mostly related to an unpleasant feeling in nasal mucosa (3 of 50 children) immediately after administration of the nasal spray. One event of vomiting was recorded.

DISCUSSION

IN dexmedetomidine was rapidly absorbed, and C_{max} was achieved in a median time of 37 minutes. Interindividual variability was, however, large, as previously reported in healthy adult volunteers.[11,20] A comparison with previous results[11] suggests that C_{max} may continue to decrease with increasing age because the dose-normalized C_{max} calculated for adult healthy volunteers was smaller (0.0060 vs 0.0086 1·liter^{-1}) than that now found in our 6- to 11-year-old pediatric patients. This is most likely linked to the larger dosing volumes needed in older subjects. The actual delivered dose volumes in our study varied from 240 to 1200 µL, which by far exceeds the volumes usually considered ideal.[21] This calls for the development of improved drug delivery systems compared to the one used in this study, if IN application is to be clinically applicable.

To evaluate the effect of age on dexmedetomidine pharmacokinetics, patients were allocated to 3 age groups. Although newborns differ from infants (0–2 years), these patients could not be included because ambulatory MRI scans are not scheduled for newborns. Similarly, there were quite few ambulatory MRI scans performed on the youngest age group. Two other age groups were based on observations on developmental pharmacology.[22] The youngest patient group had significantly higher dose-normalized peak

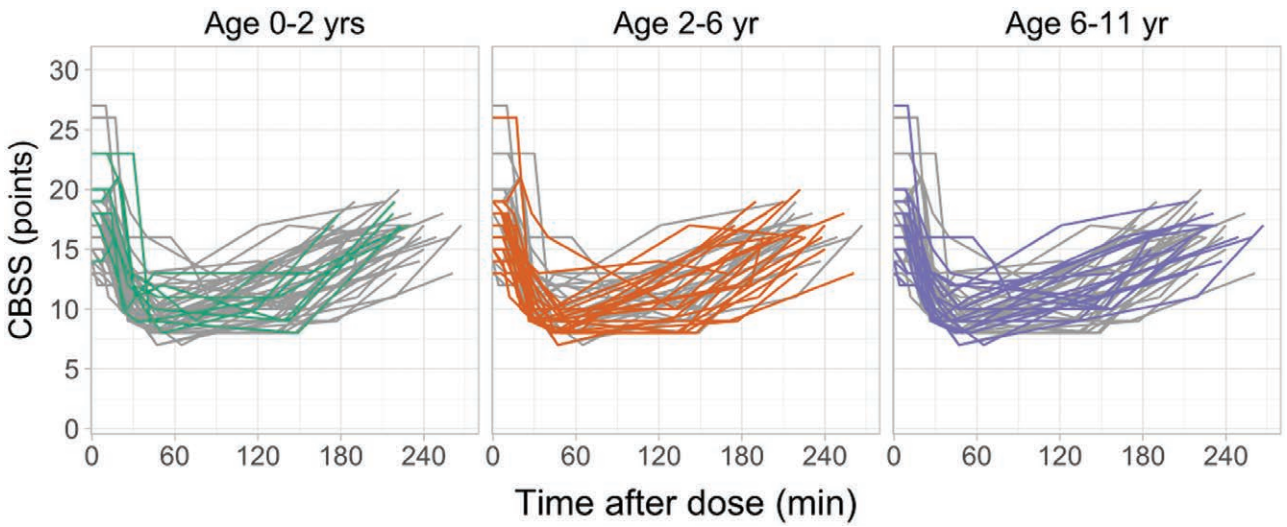

Figure 2. CBSS scores after intranasal 2–3 μg·kg^{-1} dexmedetomidine dose as nasal spray in 50 ambulatory pediatric patients in the 3 age groups. Gray curves show CBSS versus time for all 50 patients, and green, orange, and blue for 0–2, 2–6, and 6–11 y old patients, respectively. CBSS indicates Comfort-B sedation scale.

Table 3. Pharmacological Effect Parameters After Intranasal Administration of 2–3 μg kg^{-1} Dexmedetomidine

Parameter	All Patients (n = 50)	Geometric Mean, 90% CI	Age 0–2 y (n = 8)	Age 2–6 y (n = 24)	Age 6–11 y (n = 18)	*P* Value[a]
Comfort-B baseline	17 (15–18)	…	19 (18–23)	17 (15–18)	17 (15–19)	.09
Maximal reduction in Comfort-B (E_{max})[b]						
Points from baseline	−8 (6–9)	−7.5 (−6.9 to −8.5)	−9 (8–11)	−8 (6–9)	−7 (6–9)	.27
Relative change (%)	46 (38–50)	…	48 (40–56)	47 (39–50)	42 (38–51)	
Time to E_{max} (min)	45 (40–48)	…	45 (42–51)	44 (36–49)	45 (41–48)	.79
HR baseline (minute^{-1})	93 (16)	…	115 (14)	93 (9)	82 (17)	…
Maximal decrease in HR						
Beats/min from baseline	16 (8.9)	15.5 (11.3–17.6)	20 (7.8)	17 (9.3)	13 (6.2)	.90
Relative change (%)	15 (9–23)		15 (12–23)	15 (11–23)	16 (6–24)	
Spo_2 (%)	98 (93–99)	97.5 (97.2–98.8)	98 (97–99)	98 (93–99)	98 (95–98)	.24

Data are shown as median and interquartile range, except for heart rate baseline and change, which is given as mean and standard deviation.
Abbreviations: ANOVA, analysis of variance; CI, confidence interval; E_{max}, time to maximal effect; HR, heart rate; Spo_2, peripheral oxygen saturation.
[a]Comfort-B scores were tested with Kruskal–Wallis test; HR and Spo_2 with 1-way ANOVA.
[b]Before thiopental administration.

concentrations and drug exposure ($AUC_{0–4h}$) compared to the older patients.

A recent study evaluated pharmacokinetics of IN dexmedetomidine in pediatric patients (age between 6 and 44 months) undergoing cardiopulmonary bypass.[6] The patients had congenital heart disease and were anesthetized before administration of IN dexmedetomidine, both of which could have affected the disposition of dexmedetomidine. In our study, the peak concentrations (0.54 ng·kg^{-1} after a mean dose of 2.8 μg·kg^{-1}) were similar to previous findings, but t_{max} was slightly shorter. Use of IN dexmedetomidine as premedication has been studied in nonsurgical pediatric patients with dosages of 2–3 μg·kg^{-1} and the onset of IN dexmedetomidine has been described to be 10–33 minutes.[8–10] The onset of action was similar in our study (Figure 2), which coincided with the time to maximal effect. Because most of the patients received additional sedation during MRI, we were not able to evaluate the duration of sedation caused by dexmedetomidine alone.

Previously, the pharmacokinetics of IN dexmedetomidine has mainly been investigated in healthy adult volunteers.[11,20] Assuming that pediatric patients have similar nasal bioavailability as adults, we can estimate that the pediatric patients have higher $AUC_{0–4h}$ than adults because the dose-corrected $AUC_{0–4h}$ after IN dosing in the current study was 1.4 minutes·milliliter^{-1}, whereas in adults, the dose-corrected mean AUC extrapolated to infinity was 0.88 minutes·milliliter^{-1}. Considering the age dependency of the exposure, the difference seems to be even bigger in younger patients. Although we were not able to measure the absolute bioavailability in this single-period observational study, our results show that nasally applied dexmedetomidine is efficiently absorbed in children.

The average C_{max} in our study was 0.54 ng·milliliter^{-1}, which suggests that sedative concentrations were achieved after IN 2–3 μg·kg^{-1} doses of

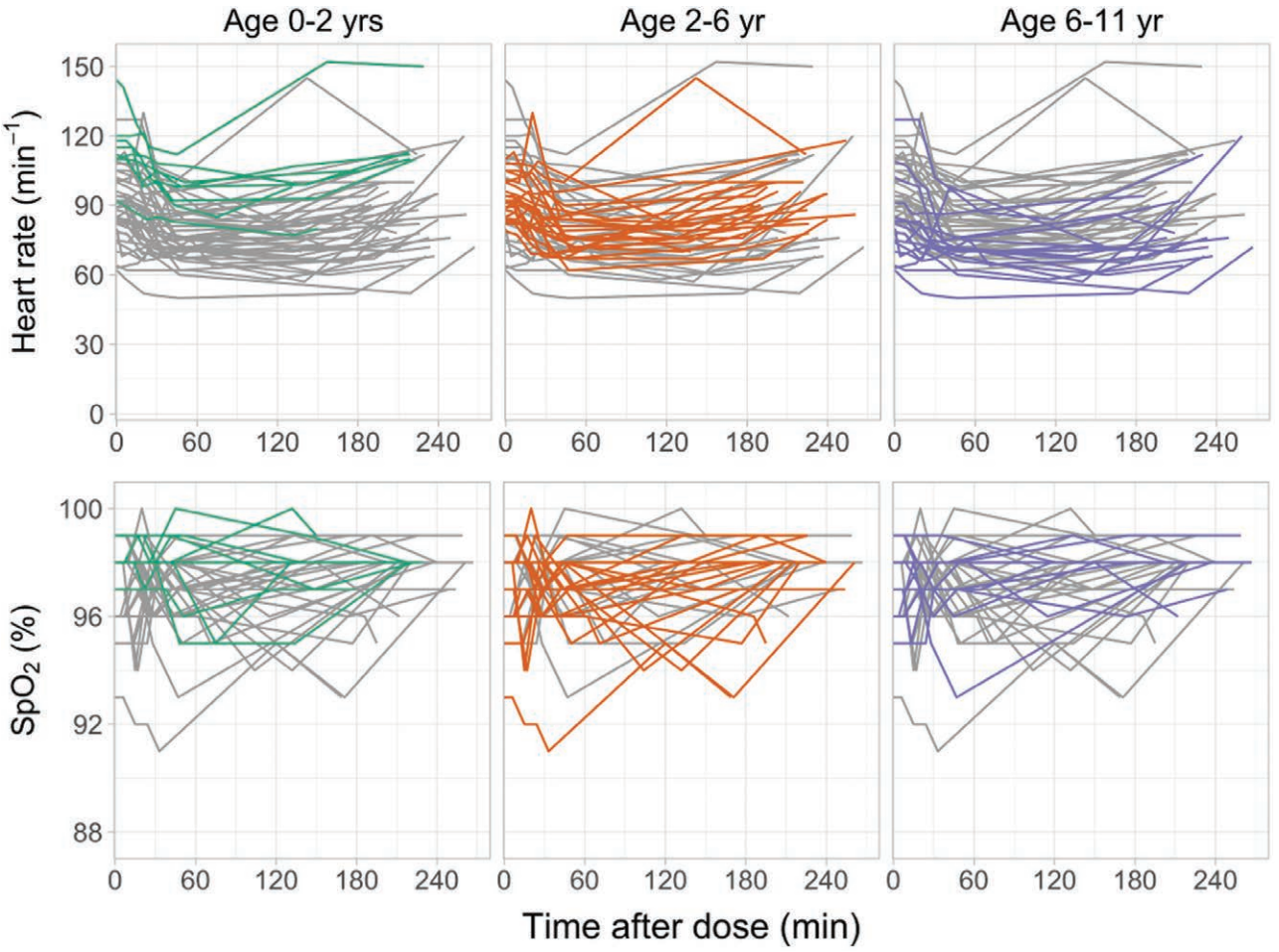

Figure 3. Vital parameters after intranasal 2–3 μg·kg^{-1} dexmedetomidine dose as nasal spray in 50 ambulatory pediatric patients in the 3 age groups. Heart rate and Spo_2 were recorded at 6 predefined times after dexmedetomidine dosing. Gray curves show heart rate or Spo_2 versus time for all 50 patients, and green, orange, and blue for 0–2, 2–6, and 6–11 y old patients, respectively. Spo_2 indicates peripheral oxygen saturation.

dexmedetomidine. The concentration–time profiles indicated that the plasma concentrations decreased quite rapidly, and higher initial doses or repeated dosing may be needed for clinical efficacy for longer procedures. Moreover, sedation with dexmedetomidine maintains patients responsive and arousable. This may be challenging in procedures where patients are expected to stay immobile. Almost all patients received thiopental due to agitation during transfer to the MRI room or for movement during the MRI; because of the need for additional sedation, we cannot state that dexmedetomidine alone was sufficient to provide sedation during an MRI.

Maximal decline in CBSS from baseline was 8 points after IN dexmedetomidine, and maximal reduction in CBSS was recorded 45 minutes after dosing. Sedation was assessed clinically acceptable as decreases of ≥6 points in CBSS have been demonstrated to indicate a good response to sedative agents in pediatric patients.[16] We found no evidence of differences in the sedative effects between the different age groups. However, the youngest age group consisted of only 8 patients, and we cannot draw any conclusions based on this finding. We chose to use the Comfort-B assessment scale because this scale is routinely used in our pediatric intensive care unit. More importantly, CBSS is an objective monitoring tool without any need for verbal or physical stimulation, which can be considered as an advantage in MRI sedation where lightly sedated spontaneously breathing pediatric patients are expected to lie immobile.

Dexmedetomidine causes individually variable hemodynamic responses and decreases HR due to its sympatholytic effects.[12,13] Our result shows that IN dexmedetomidine decreased HR on the average by 16 beats/min (by 8.9%), and this is in accordance with previously published results.[11,20] IN administered dexmedetomidine reduced HR less compared to IV dosing, which produces up to 30% decreases in HR.[2,5] Similar to the previous reports on IN dexmedetomidine, HR was reduced most in the youngest patients of 0–2 years of age. The risk of bradycardia should

be kept in mind when using high dexmedetomidine doses in young patients.

Our study has several limitations. In particular, these include small number of patients in the youngest age group, the short sampling period for dexmedetomidine plasma samples, and the common need for administration of supplemental thiopental to the patients at the later timepoints of the study to achieve acceptable sedation. Blood samples for dexmedetomidine concentration measurements were collected only up to 4 hours, based on the adult data.[11] It would be more informative to collect further blood samples more precisely and during a longer follow-up period, but because our patients were discharged after 4 hours, further follow-up was not possible. Furthermore, we had to allow a 5- to 10-minute variance in the sampling time. Nevertheless, we were able to capture informative concentration–time profiles from each patient. Our sample size was based on previous experience in the dexmedetomidine pharmacokinetics studies, but the total number of patients was low especially in the youngest age group. The selected sample size thus affects the power to compare the 3 age groups, which should be taken into consideration when evaluating the results. However, the CI evaluation shows that our primary end points have acceptable precision.

In conclusion, our results demonstrate that IN dexmedetomidine is relatively rapidly absorbed and causes significant sedation in pediatric patients. Pharmacokinetics of IN dexmedetomidine in pediatric patients show quite similar characteristics compared to adults, and our findings regarding the sedative effects are consistent with previous results published for pediatric patients. The results suggest that IN dexmedetomidine as sole agent might not be sufficient for procedural MRI sedation of pediatric patients, and combination with other sedative agents may be needed. Because the volumes of the preparation used in our study exceed the recommended volumes for IN administration, there appears to be a need for a more concentrated dexmedetomidine solution. The optimal dose and drug delivery system for IN dexmedetomidine dosing remain to be evaluated. ■

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REFERENCES

1. Heard CM, Joshi P, Johnson K. Dexmedetomidine for pediatric MRI sedation: a review of a series of cases. *Paediatr Anaesth.* 2007;17:888–892.
2. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Br J Anaesth.* 2015;115:171–182.
3. Mason KP, Zurakowski D, Zgleszewski SE et al. High dose dexmedetomidine as the sole sedative for pediatric MRI. *Paediatr Anaesth.* 2008;18:403–411.
4. Mason KP, Turner DP, Houle TT, Fontaine PJ, Lerman J. Hemodynamic response to fluid management in children undergoing dexmedetomidine sedation for MRI. *AJR Am J Roentgenol.* 2014;202:W574–W579.
5. Mason KP, Lerman J. Review article: dexmedetomidine in children: current knowledge and future applications. *Anesth Analg.* 2011;113:1129–1142.
6. Miller JW, Balyan R, Dong M, et al. Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study. *Br J Anaesth.* 2018;120:1056–1065.
7. Mekitarian Filho E, Robinson F, de Carvalho WB, Gilio AE, Mason KP. Intranasal dexmedetomidine for sedation for pediatric computed tomography imaging. *J Pediatr.* 2015;166:1313.e1–1315.e1.
8. Baier NM, Mendez SS, Kimm D, Velazquez AE, Schroeder AR. Intranasal dexmedetomidine: an effective sedative agent for electroencephalogram and auditory brain response testing. *Paediatr Anaesth.* 2016;26:280–285.
9. Yu Q, Liu Y, Sun M, et al. Median effective dose of intranasal dexmedetomidine sedation for transthoracic echocardiography in pediatric patients with noncyanotic congenital

heart disease: An up-and-down sequential allocation trial. *Paediatr Anaesth.* 2017;27:1108–1114.
10. Cozzi G, Monasta L, Maximova N, et al. Combination of intranasal dexmedetomidine and oral midazolam as sedation for pediatric MRI. *Paediatr Anaesth.* 2017;27:976–977.
11. Iirola T, Vilo S, Manner T, et al. Bioavailability of dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol.* 2011;67:825–831.
12. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology.* 2000;93:382–394.
13. Uusalo P, Al-Ramahi D, Tilli I, Aantaa RA, Scheinin M, Saari TI. Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers. *Eur J Clin Pharmacol.* 2018;74:1047–1054.
14. Mason KP. Sedation trends in the 21st century: the transition to dexmedetomidine for radiological imaging studies. *Paediatr Anaesth.* 2010;20:265–272.
15. Tschiedel E, Heck V, Felderhoff-Mueser U, Dohna-Schwake C. The influence of parents' voice on the consumption of propofol for pediatric procedural sedation—a randomized controlled trial. *Paediatr Anaesth.* 2017;27:394–398.
16. Boerlage AA, Ista E, Duivenvoorden HJ, de Wildt SN, Tibboel D, van Dijk M. The COMFORT behaviour scale detects clinically meaningful effects of analgesic and sedative treatment. *Eur J Pain.* 2015;19:473–479.
17. Bradley JS, Benziger D, Bokesch P, Jacobs R. Single-dose pharmacokinetics of daptomycin in pediatric patients 3-24 months of age. *Pediatr Infect Dis J.* 2014;33:936–939.
18. Chrysostomou C, Schulman SR, Herrera Castellanos M, et al. A phase II/III, multicenter, safety, efficacy, and pharmacokinetic study of dexmedetomidine in preterm and term neonates. *J Pediatr.* 2014;164:276.e1–82.e1.
19. Nielsen BN, Friis SM, Rømsing J, et al. Intranasal sufentanil/ketamine analgesia in children. *Paediatr Anaesth.* 2014;24:170–180.
20. Li A, Yuen VM, Goulay-Dufaÿ S, et al. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. *Br J Anaesth.* 2018;120:960–968.
21. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective-a review. *Drug Deliv Transl Res.* 2013;3:42–62.
22. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349:1157–1167.