A Phase II/III, Multicenter, Safety, Efficacy, and Pharmacokinetic Study of Dexmedetomidine in Preterm and Term Neonates

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Objective To investigate the safety, efficacy, and pharmacokinetic profile of dexmedetomidine in preterm and full-term neonates ≥28 to ≤44 weeks gestational age.

Study design Forty-two intubated, mechanically ventilated patients (n = 42) were grouped by gestational age into group I (n = 18), ≥28 to <36 weeks, and group II (n = 24), ≥36 to ≤44 weeks. Within each age group, there were 3 escalating dose levels, including a loading dose (LD, μg/kg) followed by a maintenance dose (MD, $\mu g \cdot kg^{-1} \cdot h^{-1}$) for 6-24 hours: level 1, 0.05 LD/MD; level 2, 0.1 LD/MD; and level 3, 0.2 LD/MD. The primary endpoint was the number of patients requiring sedation as determined by the Neonatal Pain, Agitation, Sedation Scale.

Results During dexmedetomidine infusion, 5% of Neonatal Pain, Agitation, Sedation Scale scores were >3, indicating agitation/pain, with 4 patients (10%) requiring more sedation and 17 (40%) requiring more analgesia. Though there was significant variability in pharmacokinetic variables, group I appeared to have lower weight-adjusted plasma clearance (0.3 vs 0.9 $L \cdot h^{-1} \cdot kg^{-1}$) and increased elimination half-life (7.6 vs 3.2 hours) compared with group II. Fifty-six adverse events (AEs) were reported in 26 patients (62%); only 3 AEs (5%) were related to dexmedetomidine. There were no serious AEs and no AEs or hemodynamic changes requiring dexmedetomidine discontinuation.

Conclusion Dexmedetomidine is effective for sedating preterm and full-term neonates and is well-tolerated without significant AEs. Preterm neonates had decreased plasma clearance and longer elimination half-life. *(J Pediatr 2014;164:276-82)*.

Providing adequate sedation and analgesia for neonatal patients with the least amount of side effects is an important component of care in the intensive care unit. Current neonatal drug regimens used to achieve these goals generally consist of combinations of benzodiazepines and opioids. However, these drugs have been associated with significant side effects, including tolerance, physical dependency, paradoxical agitation, withdrawal, inconsistent sedation, and respiratory depression.[1,2] Moreover, recent studies have demonstrated that benzodiazepines and opioids can cause neuroapoptosis and neurodevelopmental abnormalities in neonatal animals.[3,4] In some preliminary animal studies, dexmedetomidine has shown potential neuroprotective properties, including prevention of neuroapoptosis induced by other agents.[5,6]

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist with significant sedative and analgesic effects, is currently approved by the Food and Drug Administration for sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting and for sedation of nonintubated adult patients before and/or during surgical and other procedures.[7] Although dexmedetomidine has not been specifically indicated for use in pediatric populations, numerous studies have demonstrated its safety and efficacy in children.[8-14] Although dexmedetomidine can be used as the sole sedative/analgesic agent in some patients, the drug's benzodiazepine- and opioid-sparing properties have led to its more common use in conjunction with other agents.[8,13]

Initial studies have indicated that many of the pharmacokinetic (PK) variables of dexmedetomidine, including volume of distribution and elimination half-life ($t_{1/2}$),

AE	Adverse event
AUC	Area under the concentration curve
BP	Blood pressure
CL_W	Plasma clearance
HR	Heart rate
LD	Loading dose
MD	Maintenance dose
N-PASS	Neonatal Pain, Agitation, Sedation Scale
PK	Pharmacokinetic
$t_{1/2}$	Half-life

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are similar in pediatric patients and adults.[15-18] However, a pooled analysis of 4 studies found increasing plasma clearance (CL_w) of dexmedetomidine with age, indicating that age-specific dosing regimens may be required.[19] Neonatal PK data for dexmedetomidine are lacking, and in general there are important PK differences between preterm and term neonates that may affect and complicate drug therapy. The objective of this phase II/III, open-label study was to characterize the safety, efficacy, and PK of dexmedetomidine in preterm and term neonates ≥28 to ≤44 weeks gestational age.

Methods

This was a phase II/III, open-label, multicenter safety, efficacy and PK trial in preterm and term neonates. Eleven centers from North America (Children's Hospital of Pittsburgh, 13 patients; Ruby Memorial Hospital, 7 patients; Duke Children's Hospital, 5 patients; Greenville Hospital System, 3 patients; Kosair Children's Hospital, 3 patients; Loyola University Medical Center, 2 patients; Wesley Medical Centre, 2 patients; Akron Children's Hospital Medical Center, 1 patient; Georgia Health Sciences University, 1 patient; Children's Hospital of Los Angeles, 1 patient; Medical University of South Carolina, 1 patient) and 1 center from Central America (Hospital Roosevelt, Guatemala City, 3 patients) were used and received approval by their respective Institutional Review Boards and/or Ethics Committees. Written informed consent was obtained from the parent/legal guardian of each patient before any study-related activity. The study was conducted in accordance with the International Conference on Harmonization guidelines.

The study population consisted of initially intubated and mechanically ventilated neonates, gestational age ≥28 to ≤44 weeks, anticipated to require a minimum of 6 hours of continuous intravenous sedation in an intensive care setting. Patients in the following age ranges were enrolled: preterm neonates ≥28 to <36 weeks gestational age (group I) and term neonates born at ≥36 to ≤44 weeks gestational age (group II).

Exclusion criteria included weight <1 kg; heart rate (HR) <120 bpm; second- or third-degree heart block (unless a pacemaker was in place); neurologic conditions prohibiting accurate evaluation of sedation, such as catastrophic brain injury (patients who survive extensive brain damage but with residual severe neurologic impairment), or other severe mental disorders that would make the response to sedatives unpredictable and/or assessment of the Neonatal Pain, Agitation, Sedation Scale (N-PASS) unreliable; immobility from neuromuscular disease or continuous infusion of a neuromuscular blocking agent; exposure to any investigational drug within 30 days before dexmedetomidine administration; previous exposure to dexmedetomidine as part of an investigational study; and allergies to or contraindications for fentanyl, morphine, midazolam, or dexmedetomidine. In addition, because dexmedetomidine CL_w decreases with increasing severity of hepatic impairment, an alanine aminotransferase level >115 U/L (ie, 2-2.5 times the upper limit of normal) was used to exclude patients.

Patients were assigned to either age group I (≥28 to <36 weeks) or age group II (≥36 to ≤44 weeks) according to the gestational age at birth as determined by the date of the mother's last menstrual period plus the weeks after birth to the day of enrollment. The patients in each group were then sequentially assigned to 1 of 3 escalating dose levels (**Figure 1**; available at www.jpeds.com): level 1: loading dose (LD), 0.05 μg/kg; maintenance dose (MD), 0.05 μg/kg/h; level 2: LD, 0.1 μg/kg; MD, 0.1 μg/kg/h; level 3: LD, 0.2 μg/kg; MD, 0.2 μg/kg/h. Although each age group could enroll simultaneously, enrollment of each group in the next dose level could not begin until all patients had completed the previous dose level and a Data Safety and Monitoring Board, consisting of 2 independent physicians and a biostatistician, approved the dose escalation.

In the absence of data on dexmedetomidine use in preterm neonates and with only limited data on use in term neonates, we adopted a cautious study design, using a stepwise dose escalation and lower doses of dexmedetomidine than those typically used in older children and adults. This approach was expected to reduce the risk of bradycardia and hypotension, potential sympatholytic side effects of dexmedetomidine.

The study drug, dexmedetomidine hydrochloride (100 μg/mL base), was administered via a controlled infusion device. Patients were first given an LD over 10-20 minutes, followed by continuous infusion of an MD for 6-24 hours (**Figure 1**).

The need for more sedation or analgesia was determined by the clinical team and based on assessment of N-PASS values.[20] The N-PASS tool, which has been validated in both preterm and term neonates, uses 5 assessment criteria (crying/irritability, behavior/state, facial expression, extremities/tone, and vital signs), assigning a score ranging from −2 (well sedated) to +2 (experiencing pain/agitation) for each variable, to determine the effectiveness of sedation and analgesia. For each patient, the N-PASS was evaluated throughout the LD and MD periods according to the schedule shown in **Figure 1**. Significant pain or agitation was considered at an N-PASS score of >3, at which point supplemental therapy (sedation or analgesia) was indicated; sedation or analgesia also could be administered at the discretion of the investigator. Midazolam (0.05-0.15 $mg \cdot kg^{-1} \cdot dose^{-1}$) was administered for the supplemental sedation, and fentanyl (0.5-2 μg/kg bolus or 1-2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ continuous infusion) or morphine (0.025-0.1 mg/kg bolus or 0.01-0.02 $mg \cdot kg^{-1} \cdot h^{-1}$ continuous infusion) was used if more analgesia was required.[1,21]

All medications given within 24 hours before the start of dexmedetomidine, as well as concomitant and postinfusion medications, were recorded. The following medications were prohibited during dexmedetomidine infusion: sedatives and analgesics other than dexmedetomidine, midazolam, fentanyl, and morphine; continuous infusion or repeated dosing of any neuromuscular blocking agent that would preclude accurate assessment of N-PASS measurements; alpha-2 agonists/antagonists other than dexmedetomidine; and anesthetics or analgesics administered via the epidural or spinal route.

Efficacy Evaluation

The primary efficacy endpoint was the number of patients requiring midazolam for sedation during dexmedetomidine administration. Secondary endpoints included the use of medications (fentanyl or morphine) for analgesia; changes from baseline in vital signs (HR, blood pressure [BP], respiratory rate), and oxygen saturation; time spent with a total N-PASS score >3; and time to extubation from dexmedetomidine initiation.

PK Analysis

For PK analysis, 8 blood samples (0.15 mL each) were collected via arterial, venous, or capillary sampling into heparinized vacuum tubes (Figure 1). Dexmedetomidine was extracted from plasma using an automated protein extraction procedure and analyzed by high-performance liquid chromatography with tandem mass spectroscopy detection. The calibration curve range was 29.9 to 2994 pg/mL. Between-run accuracy for the method was 100.8%-103.9% of theoretical quality control concentrations, and between-precision of theoretical quality control concentrations was 3.7%-8.4%.

Descriptive statistics were used to summarize PK variables, including total exposure (area under the concentration curve [AUC]), maximal concentration, elimination $t_{1/2}$, weight-adjusted volume of distribution, weight-adjusted volume of distribution at steady state, and weight-adjusted CL_w, for each dose level and age group. Noncompartmental methods were used to estimate these standard PK variables.

Safety Evaluation

Safety evaluation included temperature, vital signs, 12-lead electrocardiogram, laboratory measurements including complete blood count and chemistry, liver function/injury, fluid input-output balance, adverse events (AEs), and treatment-emergent AEs. The individual site principal investigators were responsible for classifying the AEs according to severity as mild (transient and easily tolerated by the patient), moderate (causes discomfort and interrupts patient's usual activities), or severe (causes considerable interference with patient's usual activities and may be incapacitating or life-threatening) and according to their relationship with dexmedetomidine (ie, definitely related, probably related, possibly related, probably not related, or not related).

Statistical Analyses

Determination of sample size was based on a pairwise comparison between the low-dose group and the high-dose group. It was expected that 90% of subjects in the low-dose group and 45% of subjects in the high-dose group would require additional sedation. Thus, with 14 subjects in each group, there would be 72% power to detect the difference, assuming a 1-sided test for 2 proportions with $\alpha = 0.05$.

Because of administrative considerations, the study was completed in 2 phases, with an initial enrollment of 36 patients and subsequent enrollment of the final 6 patients in group I, dose level 3. Owing to the difficulties encountered with blood sampling in very small neonates, for the latter final 6 preterm patients, PK samples were not drawn. For efficacy, safety, and PK data, descriptive statistics are presented as counts (%) for categorical variables and mean ± SD or median (range) for continuous variables. For comparison of the percentage of patients with previous midazolam or fentanyl/morphine use vs those requiring midazolam or fentanyl/morphine during the dexmedetomidine administration, the FREQ procedure was used, followed by the Fisher exact test. Albumin and bilirubin levels were compared in the 2 groups using the Student *t* test, and PK variables were compared using the nonparametric Mann-Whitney *U* test. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina). Graphs were created in SigmaPlot version 10.0 (Systat Software, San Jose, California).

Results

The 42 patients enrolled in the study included 18 in group I and 24 in group II (Figure 2; available at www.jpeds.com). All patients completed the treatment. Most of the patients in the lowest dose level (level 1) were not included in the PK analysis because drug levels were below the limit of detection (Figure 2). The patients included in the PK-evaluable population included 4 of 14 (28.6%) from dose level 1, 11 of 14 (78.6%) from dose level 2, and 7 of 8 (87.5%) from dose level 3, suggesting that the exclusions were dose- dependent. Demographic data are presented in Table I. Six patients (14%) were enrolled after cardiopulmonary bypass, and 12 patients (29%) were enrolled after surgery.

Efficacy

Primary Endpoint. Additional sedation was administered in only 10% of the study population. Patients in group I required no extra sedation, and 4 patients in group II (17%) were given midazolam (Table II). The mean doses of midazolam were 0.10 mg/kg for dexmedetomidine dose level 1 (n = 1), 0.15 mg/kg for dose level 2 (n = 1), and 0.32 ± 0.41 mg/kg for dose level 3 (n = 2), with a total mean dose of 0.22 ± 0.26 mg/kg.

Secondary Endpoints. Additional analgesia was administered to 17 patients (40%) (Table II). Fentanyl was given in 3 patients in group I (17%). In group II, 9 patients received only fentanyl (37%), 2 received fentanyl and morphine (8%), and 3 received only morphine (12%).

N-PASS scores were collected at a total of 723 time points throughout dexmedetomidine infusion across all age groups and dose levels. Five percent of these N-PASS scores were >3 at any time point, 77% were between −5 and +3, and 18% were between −6 and −10, indicating a deeper level of sedation. In general, patients at all dose levels had a total N-PASS score of >3 for only a short time, indicating that most did not manifest signs of pain or agitation (Table II).

Across all age groups and dose levels, a total of 8 patients (20%) were extubated, at a median of 4.3 hours (range, 0.17-21 hours) after dexmedetomidine initiation.

Table I. Patient demographics*

	Group I†				Group II†				Total			
	Level 1 (n = 6)	Level 2 (n = 6)	Level 3 (n = 6)	Total (n = 18)	Level 1 (n = 8)	Level 2 (n = 8)	Level 3 (n = 8)	Total (n = 24)	Level 1 (n = 14)	Level 2 (n = 14)	Level 3 (n = 14)	Total (n = 42)
Gestational age at birth, wk, mean (SD)	30.0 (1.6)	32.5 (2.4)	32.5 (2.7)	31.8 (2.4)	38.0 (2.1)	38.9 (2.2)	39.1 (1.6)	38.7 (2.0)	34.7 (4.4)	36.1 (3.9)	36.3 (3.9)	35.7 (4.0)
Age at screening, wk, mean (SD)‡	1.00 (0.7)	0.38 (0.2)	0.8 (1.4)	0.78 (0.9)	2.12 (2.3)	1.64 (1.2)	2.23 (1.6)	1.99 (1.7)	1.64 (1.8)	1.10 (1.1)	1.7 (2.0)	1.48 (1.5)
Sex, female, n (%)	4 (67)	3 (50)	4 (67)	11 (61)	2 (25)	3 (37)	0	5 (21)	6 (43)	6 (43)	4 (29)	16 (38)
Race, n (%)												
Caucasian	3 (50)	2 (33)	5 (83)	10 (56)	7 (87)	8 (100)	6 (75)	21 (87)	10 (71)	10 (71)	11 (79)	31 (74)
Black	0	1 (17)	0	1 (6)	0	0	0	0	0	1 (7)	0	1 (2)
Other	3 (50)	3 (50)	1 (17)	7 (39)	1 (13)	0	2 (25)	3 (13)	4 (29)	3 (21)	3 (21)	10 (24)
Weight, kg, mean (SD)	1.4 (0.3)	1.7 (0.4)	1.9 (0.8)	1.7 (0.6)	3.4 (0.5)	3.0 (0.5)	3.4 (0.6)	3.3 (0.6)	2.6 (1.1)	2.4 (0.8)	2.7 (1.0)	2.6 (1.0)
CPB, n (%)	0	0	0	0	4 (50)	1 (12)	1 (12)	6 (25)	4 (29)	1 (7)	1 (7)	6 (14)
Surgery, n (%)	0	0	1 (17)	1 (6)	3 (37)	2 (25)	6 (75)	11 (46)	3 (21)	2 (14)	7 (50)	12 (29)

CPB, cardiopulmonary bypass.
*Intent-to-treat, efficacy evaluable, and safety evaluable populations are equivalent.
†Age group I included preterm neonates ages ≥28 to <36 weeks gestational age, and age group II included term neonates ages ≥36 to <44 weeks gestational age.
‡All patients were administered the study drug within 3 days of screening, and 90% within 24 hours.

Figure 3 (available at www.jpeds.com) shows the trends in mean cardiovascular and respiratory variables during dexmedetomidine infusion and for the first 6 hours after dexmedetomidine discontinuation. Comparison of baseline hemodynamic values with the lowest values measured during dexmedetomidine infusion showed that HR decreased by an average of 12% ± 9% at 7.7 ± 7.3 hours, and systolic BP decreased by 14% ± 12% at 6.5 ± 7 hours. Overall, there were no significant hemodynamic differences among the dose regimens.

Thirteen patients (31%) received midazolam, at a median of 4 hours (range, 0.5-22 hours) before starting dexmedetomidine, and 20 patients (48%) received either fentanyl or morphine at a median of 1.4 hours (range, 0-10 hours) before starting dexmedetomidine. Previous use of midazolam was tabulated against the primary efficacy endpoint, that is, the proportion of patients who received midazolam during dexmedetomidine administration. Midazolam was administered to 7% of the patients with no previous exposure to midazolam and to 15% of those patients with previous midazolam exposure ($P = .62$). In addition, given the sedative effect of opioids, previous use of fentanyl and/or morphine was also tabulated against the primary endpoint. No patients without previous exposure to these opioids received midazolam, but 15% of patients with previous exposure to opioids received midazolam ($P = .44$).

PK

PK variables are summarized in **Table III**. Overall, the patients in group I appeared to have lower CL_w (0.3 vs 0.9 $L \cdot h^{-1} \cdot kg^{-1}$), increased elimination $t_{1/2}$ (7.6 vs 3.2 hours), and increased $AUC_{0-\infty}$ dose (2049 vs 357 $pg \cdot mL^{-1} \cdot h \cdot \mu g^{-1}$) compared with those in group II.

Safety

All patients completed a minimum of 6 hours of dexmedetomidine infusion, with the majority of patients in both age groups

Table II. Summary of efficacy data

	Dose level 1 (n = 14)	Dose level 2 (n = 14)	Dose level 3 (n = 14)	Total (n = 42)
Primary efficacy				
Patients with rescue sedation, n (%)*				
Group I†	0	0	0	0
Group II†	1 (12)	1 (12)	2 (25)	4 (17)
Total	1 (7)	1 (7)	2 (14)	4 (10)
Amount of midazolam in age group II, mg/kg (n)	0.10 (1)	0.15 (1)	0.32 ± 0.41 (2)	0.22 ± 0.26 (4)
Secondary efficacy				
Patients with rescue analgesia, n (%)‡				
Group I†	1 (17)	1 (17)	1 (17)	3 (17)
Group II†	4 (50)	4 (50)	6 (75)	14 (58)
Total	5 (36)	5 (36)	7 (50)	17 (40)
Time spent with N-PASS >3, h median (range)§				
Group I†	0.5 (0-1.0)	0 (0)	0 (0-1.9)	0 (0-1.9)
Group II†	0 (0-1.0)	0.1 (0-5.0)	0.3 (0-2.0)	0.1 (0-5.0)
Total	0 (0-1.0)	0 (0-5.0)	0.2 (0-2.0)	0.0 (0-5.0)

*Rescue sedation was achieved with midazolam.
†Age group I included preterm neonates ≥28 to <36 weeks gestational age, and age group II included term neonates ≥36 to <44 weeks gestational age.
‡Rescue analgesia was achieved with either fentanyl or morphine. Fentanyl was given in 3 (17%) patients in group I and 9 (37%) patients in group II; in group II, 2 patients (8%) received fentanyl and morphine, and 3 (12%) received only morphine.
§N-PASS scores were collected at 723 time points during dexmedetomidine infusion; 5% of these 723 scores were >3, 77% were between −5 and +3, and 18% were between −6 and −10.

Table III. Summary of PK variables

	CL_w, $L \cdot hr^{-1} \cdot kg^{-1}$	AUC_{0-t}, $pg \cdot mL^{-1} \cdot h$	$AUC_{0-\infty}$, $pg \cdot mL^{-1} \cdot h$	$AUC_{0-\infty}$ dose, $pg \cdot mL^{-1} \cdot h \cdot \mu g^{-1}$	C_{max}, pg/mL	V_{dw}, L/kg	V_{ssw}, L/kg	$t_{1/2}$, h
Group I								
Level 1								
1	0.41	69	854	2049	140	1.79	2.74	3.02
2	NA	1313	NA	NA	102	NA	NA	NA
3	NA	384	NA	NA	74	NA	NA	NA
Level 2								
4	NA	142	NA	NA	34	NA	NA	NA
5	NA	508	NA	NA	123	NA	NA	NA
6	0.19	8421	11 485	2827	505	2.11	2.45	7.61
7	0.43	1012	1614	1564	116	5.70	5.89	9.11
8	NA	448	NA	NA	74	NA	NA	NA
9	NA	459	NA	NA	83	NA	NA	NA
Total	0.3	508	1614	2049	102	2.1	2.7	7.6
	(0.2-0.4)	(142-8421)	(853-11 485)	(1564-2827)	(34-505)	(1.8-5.7)	(2.5-5.9)	(3.0-9.1)
Group II								
Level 1								
10*	0.61	432	571	452	78	2.83	2.21	3.19
Level 2								
11*	NA	261	NA	NA	56	NA	NA	NA
12	1.21	406	580	272	76	4.37	3.10	2.10
13	0.97	508	725	338	67	5.33	4.64	3.93
14	0.62	702	1161	653	99	8.37	8.49	9.40
15	0.24	9428	9781	1261	965	1.98	0.54	5.73
Level 3								
16*	0.30	4369	4694	958	1019	1.30	0.47	3.03
17	0.92	2130	3189	377	192	10.99	10.91	8.24
18	0.17	7828	8030	2494	1394	0.81	0.10	3.21
19	1.40	3388	3571	227	163	6.92	5.23	3.42
20	1.03	3618	3710	255	196	2.14	1.43	1.43
21	1.47	3231	2249	192	227	2.18	9.22	1.03
22	1.06	3255	3400	270	197	4.30	4.66	2.81
Total	0.9	3231	3295	357	192	3.6	3.9	3.2
	(0.2-1.5)	(261-9428)	(571-9781)	(192-2494)	(56-1394)	(0.8-11.0)	(0.1-10.9)	(1.0-9.4)
P value, group I vs group II†	.14	.16	.94	.02	.19	.63	.94	.36

$AUC_{0-\infty}$, area under the concentration -time curve, from 0 hours to infinity; *$AUC_{0-\infty}$ dose*, area under the concentration -time curve, from 0 hours to infinity; *AUC_{0-t}*, area under the concentration-time curve, from 0 hours to final time of positive detection; *C_{max}*, maximal concentration; *NA*, not available (insufficient data to calculate the parameter); *V_{dw}*, weight-adjusted volume of distribution; *V_{ssw}*, weight-adjusted volume of distribution at steady state.
*CPB patient.
†Mann-Whitney *U* test.

receiving infusions lasting between 6 and 12 hours (Table IV). The safety profile for dexmedetomidine in neonates was typical of the critically ill, high-risk neonatal population and postoperative neonatal surgical patients. AEs were reported in a total of 26 patients (62%), including 11 (61%) in group I and 15 (62.5%) in group II. Among these, 3 patients (7%) reported a total of 4 AEs related to dexmedetomidine. Three AEs were assessed as definitely related to dexmedetomidine: diastolic hypotension in group I, dose level 2; hypertension in group II, dose level 1; and significant agitation in group II, dose level 3. One AE was assessed as possibly related to dexmedetomidine: mild, respiratory acidosis in group I, dose level 2. There were no serious AEs related to dexmedetomidine and no AEs that led to discontinuation of dexmedetomidine. No significant laboratory or electrocardiographic measurement changed during the study.

Discussion

Since the initial Food and Drug Administration approval of dexmedetomidine for the sedation of initially intubated and mechanically ventilated adults in 1999, this drug has been investigated in numerous off-label pediatric studies, most of which demonstrated a rather favorable safety and efficacy profile.[2,8-10,12-17,19,22,23] Studies describing its use in neonates are scarce and mostly retrospective in nature, however, and there no reports on the use of dexmedetomidine in preterm neonates.[24] The present study provides pivotal multicenter efficacy, safety, and PK data on dexmedetomidine use in term and preterm neonates. We found that the majority of patients were adequately sedated, with only 9% requiring extra sedation. We also found that 60% of the patients did not require additional analgesia.

Dexmedetomidine, with its 1600:1 α_2:α_1 adrenoreceptor specificity, is considered a full α_2 agonist, and activation of these receptors in the locus ceruleous results in sedation and anxiolysis.[25-27] Dexmedetomidine also exerts dose-dependent moderate primary analgesic effects through activation of α_2 adrenoreceptors in the dorsal spinal horn and a subsequent decrease in substance P release.[28]

Previous retrospective reports in neonates and infants have demonstrated that dexmedetomidine can be used alone or in conjunction with other agents to provide adequate sedation and analgesia. In an 80-patient study that included 14 neonates

Table IV. Summary of dexmedetomidine exposure and AEs

	Group I (n = 18)*	Group II (n = 24)*	Total (n = 42)
Exposure duration, h, median (range)	6.6 (6.0-24.0)	6.0 (6.0-14.4)	6.0 (6.0-24.0)
Patients with AEs, n (%)	11 (61)	15 (63)	26 (62)
Total AEs, n†	27	29	56
Significant agitation, n (%)	1 (4)	5 (17)	6 (11)
Hypokalemia, n (%)	1 (4)	4 (14)	5 (9)
Hypoalbuminemia, n (%)	3 (11)	0	3 (5)
Atelectasis, n (%)	0	2 (7)	2 (4)
Pleural effusion, n (%)	0	2 (7)	2 (4)
Hypocalcemia, n (%)	1 (4)	1 (3)	2 (4)
Diastolic hypotension, n (%)	1 (4)	-	1 (2)
Hypertension, n (%)	-	1 (3)	1 (2)
Respiratory acidosis, n (%)	1 (4)	-	1 (2)
AEs related to dexmedetomidine, n (%)‡	1 (4)	2 (7)	3 (5)
Albumin level, g/dL, mean (SD)§	2.4 (0.4)	3.1 (0.8)	-
Bilirubin level, mg/dL, mean (SD)¶	6.1 (2.5)	5.1 (4.2)	-

*Group I: preterm neonates ≥28 to <36 weeks gestational age, and Group II: term neonates ≥36 to <44 weeks gestational age.
†For each specific AE, the number and percent listed are based on the total number of AEs rather than the total number of patients.
‡In addition to the 3 AEs listed, 1 AE (age group I, dose level 2) was assessed as possibly relating to dexmedetomidine.
§Significant difference between age groups ($P = .005$, Student t test).
¶No significant difference between groups ($P = .68$).

and 66 infants after cardiac surgery, adequate sedation and analgesia were documented in 94% and 90% of cases, respectively.[13] The dexmedetomidine dose was 0.47 ± 0.21 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in neonates and 0.69 ± 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in infants ($P = .003$), with 25% of the patients requiring only dexmedetomidine and 47% requiring approximately 2.6 extra sedation/analgesic doses per 24 hours of dexmedetomidine use. These previous results support our present findings, with younger patients requiring lower dexmedetomidine doses.

Most dexmedetomidine AEs are related to the drug's sympatholytic and or parasympathomimetic profile and appear to be predictable and dose-dependent. In a previous study reported by Chrysostomou et al,[13] 34% of the patients had at least 1 episode of hypotension and 12% had at least 1 episode of bradycardia, and no respiratory AEs. In the present study, we noted no significant hemodynamic or respiratory changes that necessitated intervention or discontinuation of dexmedetomidine. HR and BP decreased by approximately 12%-14%, there were no respiratory AEs, and 20% of patients could be extubated while receiving dexmedetomidine.

The PK variables for group I appear to be different than those for the older group II patients and also different than those reported previously in children and adults.[15,17,21,29] The median weight-adjusted CL_W was 0.3 $L \cdot h^{-1} \cdot kg^{-1}$, with values reported in toddlers and older children ranging from 0.57-1.0 $L \cdot h^{-1} \cdot kg^{-1}$ and those reported in adults ranging from 0.47 to 0.68 $L \cdot h^{-1} \cdot kg^{-1}$. The volume of distribution was also significantly different, with 2.7 L/kg for group I and 3.9 L/kg for group II. Volumes of distribution in older children and adults reportedly range from 0.8 to 1.4 L/kg. The elimination $t_{1/2}$ was also longer, at 7.6 hours in group I and 3.2 hours in group II, compared with 1.8-3 hours in older children and adults.

Dexmedetomidine is metabolized extensively by the liver (phase II drug-metabolizing enzymes) to inactive metabolites through direct *N*–glucuronidation, aliphatic hydroxylation (via the cytochrome P450, 2A6 pathway), and *N*–methylation.[7] These metabolites are eliminated in the urine (95%) and feces (4%).[5] In addition, dexmedetomidine exhibits 94% protein binding to serum albumin and α_1-glycoprotein.[7] The bound fraction is decreased significantly in patients with hepatic dysfunction, possibly necessitating a dose reduction. Mean CL_w values in adult patients with mild, moderate, and severe hepatic impairment are reportedly 74%, 64%, and 53%, respectively, of those in normal healthy patients.[7] In addition, there are significant differences between patients with severe hepatic failure and healthy adult volunteers in the volume of distribution at steady state (3.2 ± 0.32 L/kg vs 2.18 ± 0.22 L/kg) and elimination $t_{1/2}$ (7.51 ± 1.80 hours vs 2.59 ± 0.39 hours).[30]

Although none of our patients had liver failure, immature hepatic drug-metabolizing capacity, particularly of the glucuronidation pathway, likely played a major role, given that many of the patients were preterm.[31] Immature glucuronidation, in addition to the lower protein and albumin levels normally seen in preterm neonates, allow for increased free, unbound dexmedetomidine. Because more than 90% of dexmedetomidine is albumin-bound, the presence of a lower albumin level (which was found in preterm neonates), along with the larger volume of distribution, can lead to a significantly increased $t_{1/2}$ and increased AUC values. Furthermore, preterm neonates exhibit decreased renal glomerular filtration compared with term neonates.[32] Although dexmedetomidine dose adjustment usually is not necessary in renal failure, when a significant amount of dexmedetomidine is free owing to lack of metabolism or lack of binding with albumin, any degree of renal insufficiency would lead to an increased $t_{1/2}$ and AUC values.

Overall, preterm neonates and, to a lesser extent, term neonates had larger volume of distribution, increased free unbound dexmedetomidine, decreased CL_w, increased $t_{1/2}$, and significantly increased AUC values. In addition, the immaturity of the blood-brain barrier in this population[32] may facilitate the sedating properties of dexmedetomidine because of its high lipid solubility and potentially higher cerebrospinal fluid concentrations. All of these factors can lead not only to increased sedative and analgesic effects of dexmedetomidine, but also to increased side effects; thus, lower doses than those recommended for older children and adults should be carefully considered at initiation of dexmedetomidine.

This study was powered to evaluate efficacy, and thus any results related to safety, including cardiorespiratory changes, should be carefully considered. In addition, several patients from group I had undetectable dexmedetomidine levels; thus, PK results could be biased, because these patients were not included in the analysis.

In conclusion, in our study cohort, dexmedetomidine was effective in sedating critically ill, initially intubated, and

mechanically ventilated preterm and term neonates and was well tolerated. The PK profile of dexmedetomidine appears to be different in neonates compared with older children and adults, exhibiting a longer $t_{1/2}$ and a larger AUC, indicating that lower doses may be required to achieve the same level of sedation and to avoid adverse effects. ■

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References

1. Hospira, Inc. Midazolam hydrochloride package insert. Lake Forest (IL): Hospira, Inc; 2005.
2. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 2000;28:2122-32.
3. Young C, Jevtovic-Todorovic V, Qin YQ, Tenkova T, Wang H, Labruyere J, et al. Potential of ketamine and midazolam, individually or in combination, to induce apoptotic neurodegeneration in the infant mouse brain. Br J Pharmacol 2005;146:189-97.
4. Sanders RD, Ma D, Brooks P, Maze M. Balancing paediatric anaesthesia: preclinical insights into analgesia, hypnosis, neuroprotection, and neurotoxicity. Br J Anaesth 2008;101:597-609.
5. Sanders RD, Sun P, Patel S, Li M, Maze M, Ma D. Dexmedetomidine provides cortical neuroprotection: impact on anaesthetic-induced neuroapoptosis in the rat developing brain. Acta Anaesthesiol Scand 2010;54:710-6.
6. Engelhard K, Werner C, Eberspächer E, Bachl M, Blobner M, Hildt E, et al. The effect of the alpha 2-agonist dexmedetomidine and the N-methyl-D-aspartate antagonist S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion in rats. Anesth Analg 2003;96:524-31.
7. Hospira, Inc. Precedex (dexmedetomidine) package insert. Lake Forest (IL): Hospira, Inc; 2008.
8. Chrysostomou C, Di Filippo S, Manrique AM, Schmitt CG, Orr RA, Casta A, et al. Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med 2006;7:126-31.
9. Easley RB, Tobias JD. Pro: dexmedetomidine should be used for infants and children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2008;22:147-51.
10. Munro HM, Tirotta CF, Felix DE, Lagueruela RG, Madril DR, Zahn EM, et al. Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth 2007;17:109-12.
11. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2007;8:115-31.
12. Chrysostomou C, Komarlu R, Lichtenstein S, Shiderly D, Arora G, Orr R, et al. Electrocardiographic effects of dexmedetomidine in patients with congenital heart disease. Intensive Care Med 2010;36:836-42.
13. Chrysostomou C, Sanchez De Toledo J, Avolio T, Motoa MV, Berry D, Morell VO, et al. Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med 2009;10:654-60.
14. Lazol JP, Lichtenstein SE, Jooste EH, Shiderly D, Kudchadker NA, Tatum GH, et al. Effect of dexmedetomidine on pulmonary artery pressure after congenital cardiac surgery: a pilot study. Pediatr Crit Care Med 2010;11:589-92.
15. Vilo S, Rautiainen P, Kaisti K, Aantaa R, Scheinin M, Manner T, et al. Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. Br J Anaesth 2008;100:697-700.
16. Diaz SM, Rodarte A, Foley J, Capparelli EV. Pharmacokinetics of dexmedetomidine in postsurgical pediatric intensive care unit patients: preliminary study. Pediatr Crit Care Med 2007;8:419-24.
17. Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. Paediatr Anaesth 2008;18:722-30.
18. Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, Schily M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology 2006;105:1098-110.
19. Potts AL, Anderson BJ, Warman GR, Lerman J, Diaz SM, Vilo S. Dexmedetomidine pharmacokinetics in pediatric intensive care: a pooled analysis. Paediatr Anaesth 2009;19:1119-29.
20. Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: Neonatal Pain, Agitation and Sedation Scale with prolonged pain. J Perinatol 2008;28:55-60.
21. Robertson J, Shilkofski N, eds. The Harriet Lane handbook. 17th ed. Philadelphia: Elsevier Mosby; 2005.
22. Su F, Nicolson SC, Gastonguay MR, Barrett JS, Adamson PC, Kang DS, et al. Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg 2010;110:1383-92.
23. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 2004;97:451-5.
24. Bejian S, Valasek C, Nigro JJ, Cleveland DC, Willis BC. Prolonged use of dexmedetomidine in the paediatric cardiothoracic intensive care unit. Cardiol Young 2009;19:98-104.
25. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. Anesthesiology 1992;76:948-52.
26. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. Anesthesiology 1989;71:75-9.
27. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003;98:428-36.
28. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 1985;22:845-58.
29. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive caret. Br J Anaesth 2002;88:669-75.
30. Cunningham FE, Baughman VL, Tonkovich L, Lam N, Layden T. Pharmacokinetics of dexmedetomidine (DEX) in patients with hepatic failure (HF). Clin Pharmacol Ther 1999;65:128.
31. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans: pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999;36:439-52.
32. 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;349:1157-67.

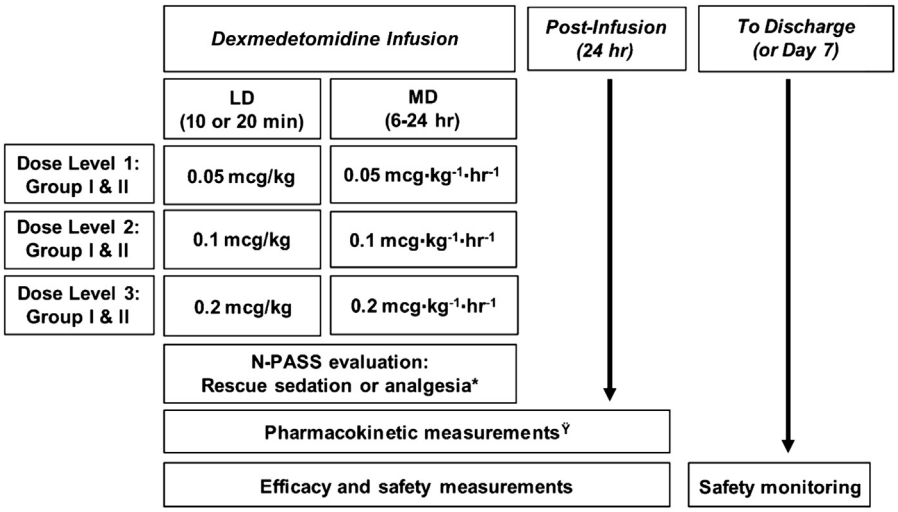

Figure 1. Schematic of the study design. *N-PASS measurements were taken before LD; at 5, 10, 15, and 20 minutes during the LD; at the start of MD, every 15 minutes for the first hour, every 30 minutes for 2 hours, and then hourly for the remainder of the MD on dexmedetomidine discontinuation and then every 15 minutes for 1 hour, every 30 minutes for the next 2 hours, every hour for the next 3 hours, and then every 4 hours until the last PK sample was obtained; and immediately before and within 5 minutes after administration of rescue midazolam, fentanyl, or morphine and within 5 minutes of every PK sample. §Samples for PK analysis were collected as follows: at the end of the LD, at 4-8 hours of the MD for patients ≥2 kg, at 10-14 hours of the MD (except group II), at the end of MD, at 10-30 minutes post-MD, at 1-2 hours post-MD for patients ≥2 kg, at 3-4 hours post-MD for patients <2 kg, and at 6-10 hours post-MD.

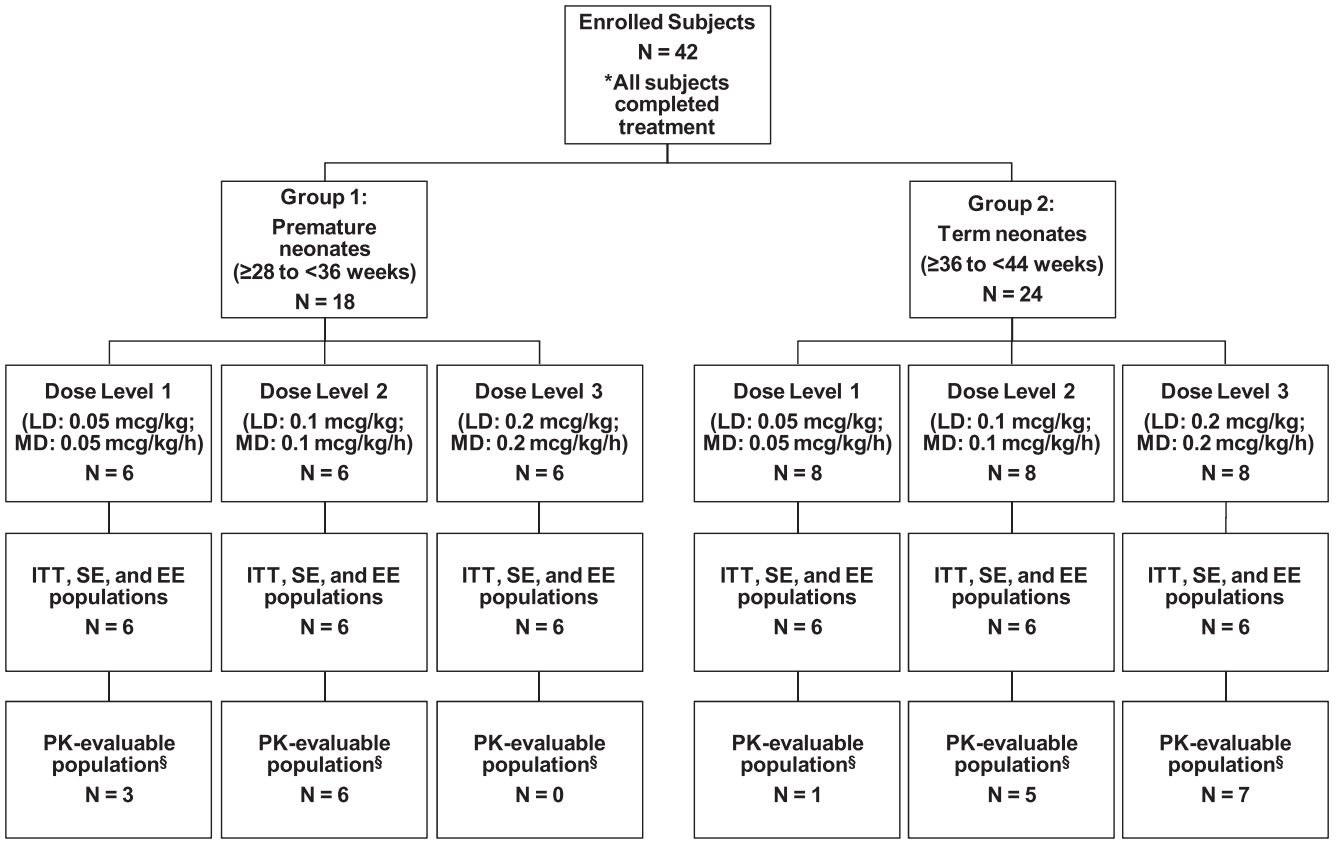

Figure 2. Patient disposition and analysis populations. §In both group I and group II, most of the patients in the lowest dose level (level 1) were not included in the PK analysis, because drug levels were below the limit of detection. *EE*, efficacy evaluable; *ITT*, intention to treat; *SE*, safety evaluable.

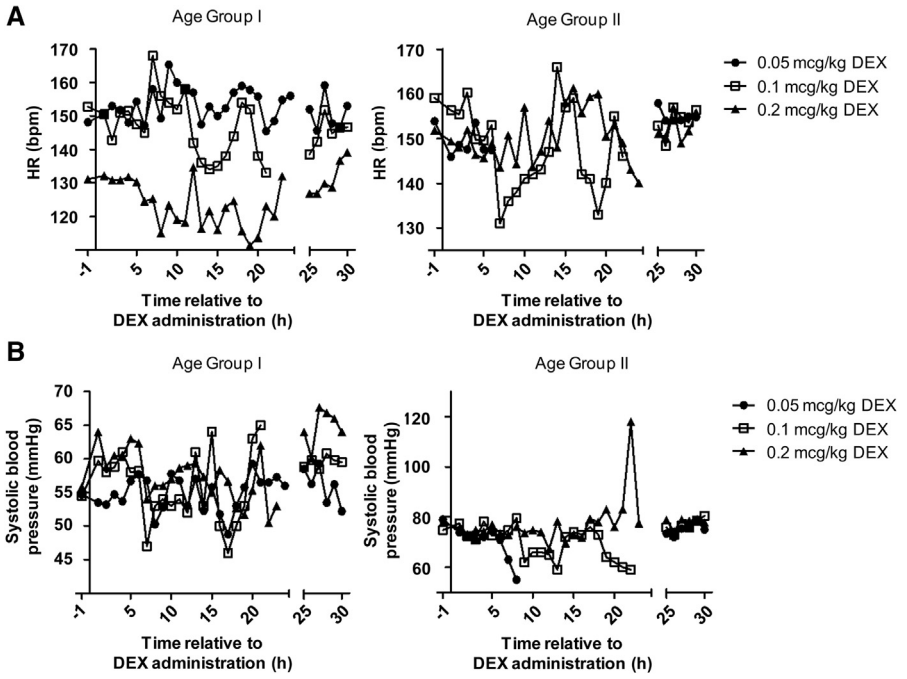

Figure 3. Changes in HR and systolic BP by age group and dexmedetomidine dose level. **A,** Average HR and **B,** systolic BP plotted as functions of time relative to dexmedetomidine administration for groups I and II at all dose levels. The gap after 24 hours indicates the start of the postinfusion period.