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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Sponsored and funded by Hospira, Inc (Lake Forest, IL). G.dR. and W.W. are employees of Hospira, the manufacturer of Precedex (dexmedetomidine HCl), and hold Hospira stock options. The sponsor was involved in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication. Assistance in the preparation of this manuscript was provided by MMS Holdings Inc (editing for grammatical errors, preparation of **Tables** and **Figures**, and proper formatting for references). The other authors declare no conflicts of interest.

Registered with ClinicalTrials.gov: NCT01159262 and NCT01508455.

 http://dx.doi.org/10.1016/j.jpeds.2013.10.002

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.