RESEARCH PAPER

Prolonged Dexmedetomidine Infusions in Critically Ill Infants and Children

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Objective: To present our institutional experience with prolonged dexmedetomidine (DEX) infusions in critically ill infants and children.

Design: Retrospective medical chart review between January 1, 2007 and December 1, 2007.

Setting: Tertiary care pediatric teaching hospital.

Participants: Infants and children (up to 18 years of age) who received DEX for a duration greater than 24 hours.

Main Outcome Measures: DEX dosing schema and rationale for use. Indices describing DEX efficacy and tolerability including change in patient-specific sedation scores, change in blood pressure and heart rate, and change in conventional analgesia and sedation requirements.

Results: Twenty-nine patients (age 5.32 ± 6.1 y) were evaluated. DEX therapy was initiated at 0.36 ± 0.16 mcg/kg/hour. One-third of patients received a loading dose (0.5-1 mcg/kg) prior to the start of the infusion. Duration of DEX therapy was 110 ± 83 hours (range 32-378 hours; median 76 hours). Rationale for adding DEX to sedation regimens included: intent to extubate (*n*=12), intent to reduce benzodiazepine and opioid use (*n*=10), exclusive continuous sedation (*n*=5) and management of drug withdrawal (*n*=2). Sedation scores remained stable during DEX therapy. Use of conventional analgesia and sedation was generally reduced while receiving DEX. Initiation of therapy was associated with a transient, yet statistically significant reduction in HR (from 120 ± 28 bpm to 107 ± 27 bpm) (*P* = 0.002), but without a change in blood pressure.

Conclusions: Prolonged DEX infusions were associated with a reduction in concomitant analgesia and sedation medications. DEX was well tolerated with the exception of heart rate, which decreased during the initiation of therapy but may not represent a clinically significant reduction.

Key words: *Children, Dexmedetomidine, Sedation.*

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Dexmedetomidine HCl (DEX; Precedex, Hospira Inc, Lake Forest Ill, USA) is a potent alpha-2-adrenergic agonist that imparts sedative, analgesic and anxiolytic effects without causing respiratory depression. DEX may be helpful in reducing traditional sedative/analgesic use while still allowing for a calm, comfortable, and cooperative state. The pharmacologic effect of DEX is mediated through all four known subtypes of alpha-2 adrenergic receptors (α_2A, α_2B, α_2C, α_2D)(1) and currently is FDA approved as a sedative for short-term use (periods not exceeding 24 hours in duration) in adults undergoing mechanical ventilation. Based on efficacy in adults, DEX is now being considered in children. Pediatric experience with DEX has been predominately in the form of case series and small reports and has focused mainly on short term or procedural use(2-10). Little data is available describing extended infusions in children (11-13).

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We report our experience with prolonged (greater than 24 hours) use of DEX in critically ill children

and attempt to characterize indications, dosing schema, use of as needed sedation, hemodynamic effects and clinical sedation scores associated with this therapy.

METHODS

This was a retrospective chart review of all infants and children (up to 18 years of age) who received DEX for greater than 24 hours in duration between January 1, 2007 and December 1, 2007. Patients were identified from the pharmacy database (Epic Hyperspace (Epic Rx) Systems Cooperation®) at The Children's Hospital (TCH), Denver, Colorado. This study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board and informed parent/subject consent was waived.

Data collection included patient demographics and indices related to DEX efficacy and tolerability. Primary outcomes included DEX dosing schema (initial dose, maximum dose and duration), indication/rationale for DEX use, change in patient-specific sedations scores, change in hemodynamic parameters (systolic and diastolic blood pressure, and heart rate) and number of conventional as needed sedation doses required before, during and after DEX therapy. The number of "as needed" sedation doses required during DEX therapy was calculated by adding the number of doses required per patient per day and then taking the mean of that number. Adequacy of sedation was assessed using a numerical scoring system developed and validated at the Penn State Children's Hospital for mechanically ventilated children(14). This scoring system allows the medical team to designate a patient-specific sedation goal. The bedside nurse then assigns a sedation score based on the behavior of the ventilated child. Currently, only the Pediatric Intensive Care (PICU) uses this numerical tool in their mechanically ventilated patients. Sedation was scored multiple times throughout the day and was averaged over 12-hr periods for our analysis.

The daily dose of DEX (mcg/kg/hour) was calculated by averaging the 24-hr dosing requirement of each patient. Because DEX is often used to aid in successful extubation, our secondary intention was to describe data regarding mechanical ventilation requirements and attempts at extubation. The use and titration of DEX was completely at the discretion of the medical team and the decision to extubate was based on assessment by the unit intensivist. Hemodynamic variables (blood pressure [mmHg] and heart rate [beats per minute; bpm]) were documented before and during DEX infusions. All medical record charting at TCH is electronic and patient-specific variables from bedside monitors are downloaded hourly. Since all subjects had continuous monitoring of hemodynamic variables, we averaged patient-specific data every 12 hours during DEX therapy. We elected to categorize patients based on unit location (cardiac, pediatric or neonatal ICU) because each unit is directed by separate and distinct medical teams, and the physiology and diagnoses of patients are uniquely tied to their location, This location classification then allowed for comparison of prescribing practices between physician groups and comparison of efficacy and tolerability of DEX based on major underlying disease state(s).

Data are presented as mean ± standard deviation (SD) or percentage where appropriate. Median data are reported if significant skewness was detected. A two-tailed, paired *t*-test of means was performed to determine statistical change in hemodynamic variables. A *P* value less than 0.05 was considered statistical significant for any given measure.

RESULTS

A total of 40 patients received DEX during the study period. Eleven patients (*n*=7, PICU patients; *n*=4, CICU patients) were excluded because they received DEX for less than 24 hours duration, leaving 29 patients (*n*=14, PICU; *n*=15, CICU) for analysis. Mean age of study population was 5.32±6.1 years with a range of 0.42-18 years. Patients in the CICU subgroup were younger than patients in the PICU subgroup (3.2±5.6 yrs *vs* 7.6±5.9 yrs, respectively). There were more males (59%) than females in the study group. Ninety-three percent of patients were mechanically ventilated at the start of DEX therapy (86% in PICU and 100% in CICU). The 2 patients who were spontaneously breathing at the initiation of DEX were adolescents (13 yrs and 15 yrs) and had a

diagnosis of sepsis and Steven's Johnson syndrome, respectively.

The primary diagnoses of the study population were heterogeneous, and included correction/ palliation of a congenital heart defect (*n*=10), respiratory failure requiring mechanical ventilation for reasons other than pneumonia (*n*=9), trauma (*n*=3), respiratory failure requiring mechanical ventilation for pneumonia (*n*=3), sepsis (*n*=2) and post-operative heart transplant (*n*=2). The rationale for adding DEX to sedation regimens included: intent to transition towards extubation (*n*=12), intent to reduce benzodiazepine and opioid dosing (*n*=10), exclusive continuous sedation (*n*=5) and management of drug withdrawal (*n*=2).

DEX Dosing. The decision to use a loading dose was at the discretion of the prescribing physician. While our institution provides general dosing recommendations of 0.3-0.7 mcg/kg/hour as a continuous infusion dose, the medical team was responsible for all dose titrations. DEX therapy was initiated at a mean dose of 0.36±0.16 mcg/kg/hour (range: 0.1-0.75). ***Figure* 1** illustrates the mean daily DEX dose requirements (mcg/kg/hour). One-third of patients (8/29) received a loading dose (0.5-1 mcg/kg) prior to the start of the continuous infusion (4/14 PICU patients and 4/15 CICU patients). When daily infusion doses were averaged, the maximum dose was 0.65±0.34 mcg/kg/hour (range: 0.2-1.5), with similar values in the PICU (0.61±0.37 mcg/kg/hr) and CICU (0.67±0.32 mcg/kg/hr). The mean duration of DEX therapy was 110±83 hours (range: 32-378 hours; median=76 hours) and was twice as long in the PICU patients (149±102 hrs) as compared to the CICU patients (72.6±34.6 hrs). Overall, sixteen patients (55%) had their DEX infusion slowly tapered downward as therapy was ending. The decision to taper the DEX infusion was directed by the medical team and was equally likely in the CICU and PICU subgroups. In general, the taper lasted from 1-4 days in duration and typically represented 25-50% dose reductions per day. Of the 14 patients who received DEX therapy for longer than 72 hours, we observed a taper in 13 (93%). When DEX was used as the exclusive continuous sedation agent (*n*=5 patients), the mean dose ranged from 0.3-0.48 mcg/kg/hr and none of the patients received a loading dose. The mean duration of DEX therapy in those patients was 89 hours (range 32-168 hrs).

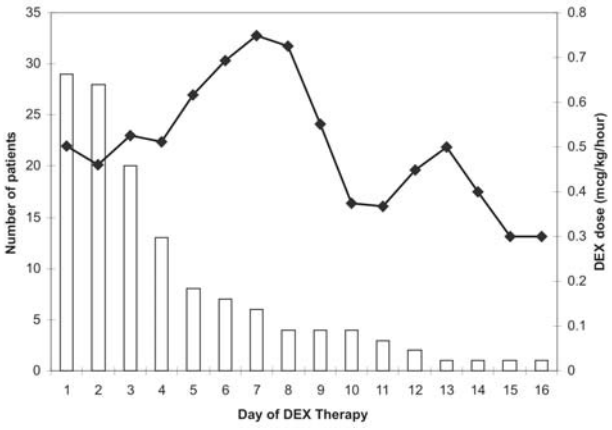

FIG.1 *Mean daily dexmedetomidine (DEX) dose (mcg/kg/hr) over time (solid line) and number of patients receiving DEX infusions (open bars) per day.*

Sedation. The majority of patients were receiving baseline sedation medications prior to the initiation of DEX with a combination of continuous infusion midazolam (*n*=16), intermittent midazolam or lorazepam (*n*=19), continuous infusion opioid (*n*=22), intermittent opioid (*n*=20) or chloral hydrate (*n*=14). During DEX therapy, sedation scores were recorded in all twelve of the mechanically ventilated PICU patients. On average, patients were maintained at a sedation level between 2 and 3 during the first 192 hours (8 days) of therapy and then decreased to a sedation level of 1-2 for the remaining days of therapy. This represents a trend toward more wakeful state in those patients receiving therapy beyond 8 days.

Additional as needed doses of sedation were recorded the day prior to starting DEX therapy, during the DEX infusion and then again the day after DEX therapy was discontinued. Patients received a variety of medications which included benzodiazepines (midazolam, lorazepam), opioids (fentanyl, morphine, hydromorphone) and chloral hydrate. Overall, the number of as needed doses was higher during DEX therapy compared to before and after, and this trend remained evident in the subgroup of patients who received DEX as exclusive continuous sedation **(*Table* I).** Despite an increase in as needed doses, the overall amount of sedation (continuous

TABLE I COMPARISON OF SEDATION REQUIREMENTS BETWEEN STUDY AND DEXMEDETOMIDINE GROUPS

Sedation requirement according to DEX therapy	Entire study (*n*=5)	DEX as exclusive continuous sedation (*n*=5)
Number of needed BZD doses/day per patient		
1 d before initiation	1.8±2.3	1.3±0.9
During DEX therapy	2.2±1.7	1.9±1.3
1 d following discontinuation	0.9±1.2	1.3±1.3
Number of needed opioid doses/day per patient		
1 d before DEX initiation	2.2±2.4	1.8±2.4
During DEX therapy	2.6±1.3	1.3±0.7
1 d following discontinuation	0.9±1.4	1.5±3
Number of chloral hydrate doses/day per patient		
1 d before DEX initiation	0.8±1	0.4±0.5
During DEX therapy	1±1.24	1.3±1.9
1 d following discontinuation	0.8±1.3	1±1.4

** All data presented as mean ± SD. Dose of sedation requirement was calculated by adding the number of doses required per patient per day and then taking the mean of that number; d-day.*

sedation plus as needed sedation) was generally reduced during DEX therapy. Of the patients who were receiving continuous opioid and BZD therapy when DEX was initiated, 54% (*n*=11) and 45% (*n*=11) were able to completely discontinue their continuous opioid and BZD infusions during DEX therapy, respectively. Another 18% (*n*=4) and 4.5% (*n*=1), respectively, were able to reduce their continuous infusion requirements by more than 50%. Six patients (4 opioid patients and 2 BZD patients) required an increase in infusion doses even after starting DEX therapy.

Hemodynamic effects. Systolic and diastolic blood pressures, along with heart rate (HR), were documented hourly and then averaged over 12-hour periods during DEX therapy. Overall, patients appeared to tolerate DEX initiation well **(*Fig.* 2)**. At day 4, there appears to be a reduction in both systolic and diastolic pressures in the CICU subgroup, but this represents the exit of older patients and re-calibration of means to reflect a younger group of remaining subjects. A transient, yet statistically significant decrease in HR was associated with the first 24 hours of DEX therapy. Baseline (24 hrs prior

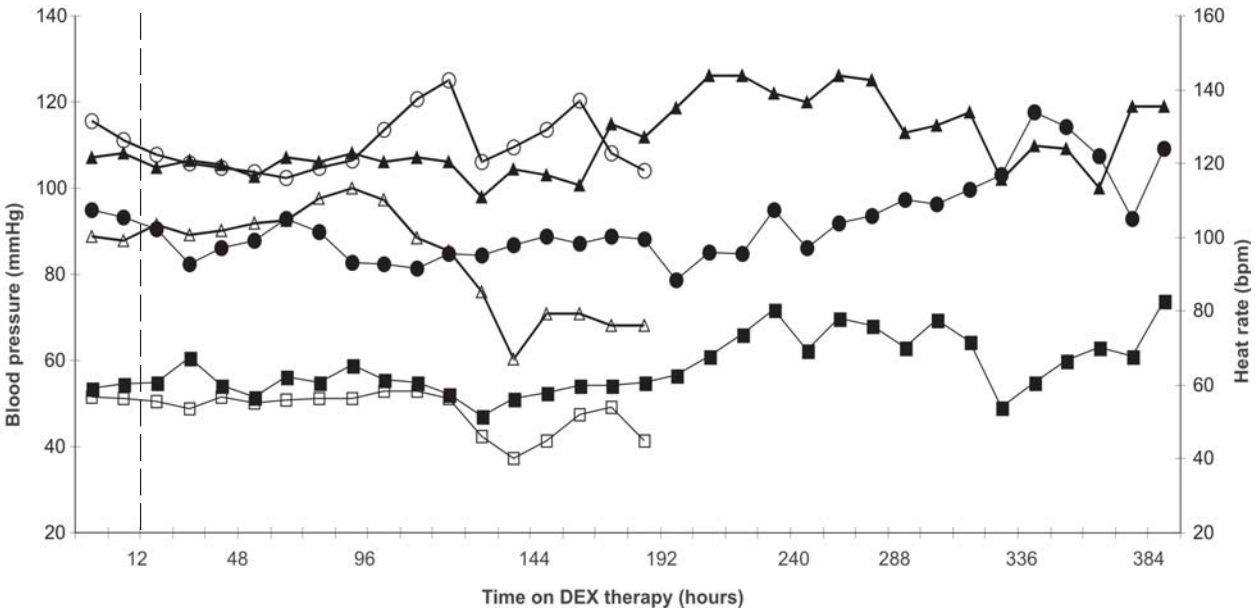

FIG. 2 *Mean heart rate (circle) systolic (triangle) and diastolic (square) blood pressure of study group (pediatric intensive care subject = solid markers and cardiac intensive care subjects = open markers). Each marker represents a 12-hour block of time. Dotted line represents start of DEX infusion and first 12-hour blood pressure measurement on therapy.*

to DEX initiation) HR was 120±28 bpm and decreased to 107±27 bpm 24 hour post DEX initiation (P=0.002). This association was consistent in both the CICU and PICU subgroups. Since rapid intravenous infusion or bolus dosing of DEX has been associated with a higher risk of hemodynamic instability(1), we separately analyzed those patients (n=8) who received a bolus dose of 0.5-1 mcg/kg prior to starting continuous therapy. However, we did not find the same association. Systolic, diastolic and HR values remained stable from 12 hours prior to DEX therapy to 24 hours after DEX initiation (P= 0.56, P=0.56, P=0.78, respectively).

Extubation rates. Twelve patients were started on DEX therapy considering possible extubation while 15 mechanically ventilated patients were started on DEX for other indications. When we excluded chronically ventilated children with tracheostomy from analysis (n=3) and compared extubation rates between these two groups, more patients in the intent-to-extubate group failed their first extubation attempt (30% failure, n=3/10) compared to the rest of the study patients (7% failure, n=1/14). These rates are comparable to our overall extubation failure rate of 6%. Of the patients who failed their first extubation attempt after starting DEX (n=4), 3 patients were from the PICU and 1 was from the CICU and two of the patients had a primary diagnosis of pulmonary hypertension. Of the 23 patients who were acutely mechanically ventilated, 6 (26%) were extubated within 72 hours of starting DEX, with 3 patients in the intent-to-extubate group and 3 in the "other indications" group. Overall, patients were mechanically ventilated 1.6±8.7 day (range; 8 to 35 days) after stopping DEX therapy, which illustrates that some patients were successfully extubated prior to the discontinuation of DEX.

DISCUSSION

We report the use of prolonged DEX infusions in infants and children at doses of 0.1-1.5 mcg/kg/hour for 110±83 hours (range: 32-378 hours). Overall, concomitant opioid and benzodiaze-pine therapy was reduced and DEX was generally well tolerated. In most patients (41%), DEX was initiated as an adjunctive to conventional sedation in patients close to extubation in an effort to minimize the risk of respiratory depression. In 34% of patients, DEX was initiated with the intent to reduce/spare benzodiazepine and opioid requirements. Overall, the use of as needed sedation actually increased during DEX therapy, but this was most likely due to the fact that the majority of patients were able to completely stop or substantially reduce their concomitant opioid and BZD infusions during this same period. Thus, the total amount of opioid and BZD could be reduced during DEX therapy. Nevertheless, there was a small subgroup of children in the present study that required an increase in overall sedation, despite the addition of DEX.

Changes in blood pressure and HR (bradycardia) have previously been reported in patients receiving DEX, especially when a loading dose is prescribed(3,15-17). DEX initiation was not associated with any significant change in blood pressure. However, DEX was associated with a statistically significant reduction in HR, with a mean HR reduction of 13 bpm from baseline (24 hours prior to DEX) to 24 hours after the initiation of DEX. This drop in HR may represent an important hemodynamic effect of DEX or may correspond to improved sedation with less agitation. Arguably, a mean HR reduction of 13 bpm may not denote a clinically significant decrease. We did not observe the same impact on HR in the small group of patients (n=8) who received a DEX loading dose prior to the initiation of a continuous infusion. One plausible explanation for this lack of effect may be selection bias. It is possible that those patients who received a DEX bolus were deemed more hemodynamically stable by the medical team and hence judged as better candidates for a bolus, compared to the rest of the study group.

DEX is an appealing agent to use in patients close to extubation because of its relative lack of respiratory drive depression. Therefore, we analyzed the association of extubation failure/success and the rational of DEX initiation. We observed a higher extubation failure rate (30%) in those patients specifically started on DEX with the intent to extubate, compared to the rest of the study group requiring mechanical ventilation (7% failure rate). A possible explanation for the higher failure rate in the

WHAT IS ALREADY KNOWN?

- Dexmedetomidine has short-term efficacy and tolerability in infants and children and has sedative, analgesic and anxiolytic effects, without causing respiratory depression.

WHAT THIS STUDY ADDS?

- Dexmedetomidine infusions in infants and children for 110 ± 83 hours were associated with an overall reduction in concomitant opioid and benzodiazepine therapy but associated with fall in heart rate during the first 24 hour of therapy.

intent-to extubate group may be due to the higher proportion of PICU patients in that group (60%) compared to the rest of the study group (50%). The PICU patient population is generally more diverse in terms of pulmonary pathology while the CICU group tends to be more homogenous and extubates quickly during the post-operative period. Additionally, the CICU physician group uses a ventilator weaning protocol, unlike the PICU physician group. This weaning protocol may aid in assessing patient readiness for extubation. However, one can not overlook the possibility that the use of DEX may change the way a child exhibits their readiness to extubate. It is possible that a child may appear alert and cooperative, yet may in fact be too sedated for a successful extubation. As only 4 patients had documented sedation scores in the planned extubation group, we are unable to relate sedation score to success of failure of extubation.

There were limitations to our study that are attendant to any retrospective review. Since this was an observational analysis, we were not able to control for parameters that may have impacted outcomes. In particular, the use of DEX was completely at the discretion of the intensivist – including the decision to use a loading dose and all dosing titration maneuvers. Additionally, this was an open label study and did not include a control group, therefore we can report only associations of DEX with outcomes and can not assume any causality. Furthermore, the decision to use additional sedation medications as well as the readiness for extubation was at the judgment of the medical team. While DEX offers the clinician another choice for continuous and titratratable sedation in the ICU, it does not seem to be the universal solution for all children requiring sedation and analgesia. In an effort to describe the best candidate for DEX, controlled prospective and blinded trials must be performed.

Contributors: PDR was responsible for the study idea, design and data analysis. MP collected and co-analyzed all data and reviewed the manuscript. ELD reviewed and edited the manuscript; provided key insight to ICU management issues; contributed important data interpretation and intellectual content. All authors approved the final content of the manuscript.

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