CASE REPORT

Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU

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ABSTRACT

This retrospective study aims to report on the use of dexmedetomidine to treat opioid withdrawal following sedation during mechanical ventilation in a cohort of infants. Seven infants in the pediatric intensive care unit of a tertiary care center, ranging in age from three to 24 months (12.4 ± 8.2 months) and in weight from 4.6 to 15.4 kgs (9.9 ± 4.2 kgs), had received a continuous fentanyl infusion, supplemented with intermittent doses of midazolam for sedation, during mechanical ventilation. Withdrawal was documented by a Finnegan score ≥ 12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/hr, followed by an infusion of 0.5 μg/kg/hr.

Dexmedetomidine effectively controlled the signs and symptoms of withdrawal in the seven patients. Subsequent Finnegan scores were ≤ 7 at all times (median 4, range 1 to 7). Two patients required a repeat of the loading dose and an increase of the infusion to 0.7 μg/kg/hr. These two patients had received higher doses of fentanyl than the other five patients (8.5 ± 0.7 versus 4.6 ± 0.5 μg/kg/hr, $p < 0.0005$). No adverse hemodynamic or respiratory effects related to dexmedetomidine were noted.

This report involves the largest cohort of patients to receive dexmedetomidine in the treatment of withdrawal following opioid and benzodiazepine sedation during mechanical ventilation. We conclude that dexmedetomidine offers a viable option for such issues in the pediatric intensive care unit (PICU) setting.

Key words: dexmedetomidine, pediatric, opioid, opioid withdrawal

INTRODUCTION

Given the potential for long-term consequences of both physical and emotional pain, there is now an appropriately heightened awareness of the need to provide analgesia, sedation, and anxiolysis during acute illness, particularly in children. As a result of these concerns, benzodiazepines and opioids are often administered to provide sedation and analgesia in the pediatric intensive care unit (PICU) setting. With prolonged administration, tolerance and physical dependence may develop, and if these agents are abruptly discontinued withdrawal symptoms are likely to occur.[1] Options for the management of these problems include slowly tapering intravenous administration, conversion to subcutaneous administration, or switching to oral medications.[1,2] Although these strategies may prevent withdrawal, therapies are also needed for patients manifesting acute signs and symptoms of withdrawal.

The α_2-adrenergic agonist dexmedetomidine (Precedex®, Hospira, Lake Forest, IL) was first released for clinical use in December 1999. It is currently FDA approved for sedation of adults during mechanical ventilation for up to 24 hours. In addition to its use for sedation during mechanical ventilation, there are anecdotal reports regarding its use for the treatment of withdrawal in the ICU setting in both adult and pediatric patients.[3-6] We present our experience with the use of dexmedetomidine to treat opioid withdrawal following the prolonged administration of fentanyl for sedation of infants and children during mechanical ventilation.

METHODS

Review of these cases and presentation of these patients was approved by the Institutional Review Board of the University of Missouri. Patients were identified as having received dexmedetomidine for the treatment of opioid withdrawal. Demographic data included age, weight, and gender. Additional data included the duration of the fentanyl infusion, the maximum fentanyl-infusion rate, and Finnegan scores prior to and after the administration of dexmedetomidine. As part of our routine practice, patients who manifest withdrawal are assessed every four to six hours using the Finnegan scoring system to assess the severity of withdrawal and the response to therapy.[7,8] Demographic and other parametric data are presented as the mean ± SD, while nonparametric data (Finnegan scores) are presented as the

median and range. A nonpaired t-test was used to compare the maximum fentanyl-infusion rate in patients who required a repeat bolus dose of dexmedetomidine and an increase in the infusion rate to control withdrawal versus those who did not. A paired t-test was used to compare heart rate, systolic blood pressure (SBP), and respiratory rate before and after the administration of the dexmedetomidine bolus dose.

RESULTS

Seven patients were identified who had received dexmedetomidine to treat opioid withdrawal. The patients ranged in age from three to 24 months (12.4 ± 8.2 months) and in weight from 4.6 to 15.4 kgs (9.9 ± 4.2 kgs). The patients had received a continuous fentanyl infusion, supplemented with intermittent doses of midazolam for sedation, during mechanical ventilation for respiratory failure due either to a primary pulmonary infection or following surgery for congenital heart disease. The patients were breathing spontaneously, having undergone successful tracheal extubation 24 to 48 hours prior to starting dexmedetomidine. The duration of the fentanyl infusion and midazolam administration ranged from four to nine days (5.9 ± 1.7 days). The maximum fentanyl-infusion range was 4 to 9 μg/kg/hr (5.7 ± 1.9 μg/kg/hr). The fentanyl infusion was gradually decreased over 24 to 48 hours in three patients and discontinued without weaning in the other four patients. Supplemental midazolam administration varied from 0.21 to 0.54 mg/kg/day in divided doses (0.37 ± 0.12 mg/kg/day). All seven patients manifested signs and symptoms indicative of severe withdrawal, with a Finnegan score ≥ 12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/hr over five to 10 minutes, followed by an infusion of 0.5 μg/kg/hr. Two patients required a repeat of the loading dose and an increase of the infusion to 0.7 μg/kg/hr. These two patients had received higher doses of fentanyl than the other five patients (8.5 ± 0.7 versus 4.6 ± 0.5 μg/kg/hr, $p < 0.0005$). The signs and symptoms of withdrawal were effectively controlled by dexmedetomidine. Following dexmedetomidine, Finnegan scores were ≤ 7 at all times (median 4, range 1 to 7). No adverse hemodynamic or respiratory effects related to dexmedetomidine were noted. With the bolus dose of dexmedetomidine, the heart rate decreased from 158 ± 12 to 138 ± 9 beats/min, $p = 0.02$, and the respiratory rate decreased from 40 ± 8 to 33 ± 6 breaths/min, $p = 0.0004$. No statistically significant change in SBP was noted (91 ± 11 to 87 ± 9 mmHg). SBP decreased in five patients and increased in two patients following the dexmedetomidine loading dose. No patient manifested a heart rate or SBP below the fifth percentile for age during the use of dexmedetomidine. The dexmedetomidine infusion was decreased in increments of 0.1 μg/kg/hr every 12 to 24 hours. No rebound hypertension was seen with this weaning regimen.

DISCUSSION

Dexmedetomidine is an α_2-adrenergic agonist. Although both dexmedetomidine and clonidine possess specificity for the α_2 versus the α_1 receptor, the specificity is greater with dexmedetomidine (200:1 for clonidine versus 1600:1 for dexmedetomidine).

An additional difference is the shorter half-life of dexmedetomidine (two to three hours) when compared with clonidine (12 to 24 hours), allowing for its titration by continuous infusion and a more rapid reversal of its effects should problems arise. Previous clinical and animal studies have reported the successful use of clonidine to treat withdrawal from various agents, including opioids, cannabinoids, and ethanol.[9-16] Baumgartner and Rowen[9] randomly assigned 50 adults undergoing ethanol withdrawal to receive either transdermal clonidine or chlorodiazepoxide. Therapy was deemed effective with either treatment arm, as no patient developed seizures or progressed to delirium tremens. The group receiving clonidine had a better response to therapy (assessed using the Alcohol Withdrawal Assessment Scale), less anxiety (assessed using the Hamilton Anxiety Rating Scale), and improved control of heart rate and blood pressure. Dobrydnjov et al.[10] evaluated the efficacy of either intrathecal or oral clonidine to attenuate postoperative alcohol withdrawal syndrome in 45 alcohol-dependent patients. The patients had undergone transurethral resection of the prostate, performed using spinal anesthesia. The patients were randomized to receive preoperative oral diazepam, intrathecal clonidine, or oral clonidine. Either oral or intrathecal clonidine was superior to oral diazepam. Twelve patients in the diazepam group had symptoms of alcohol withdrawal, compared with two in the intrathecal-clonidine group and one in the oral-clonidine group. Additionally, two patients receiving diazepam went on to develop delirium tremens. Patients in the oral diazepam group also manifested greater hemodynamic instability, with tachycardia and elevated blood pressure developing 24 to 72 hours after surgery.

Animal data also support the potential role of dexmedetomidine to treat withdrawal phenomena. Riihioja et al.[17-20] demonstrated that dexmedetomidine effectively controls ethanol withdrawal behavior, manifesting as hyperactivity of the sympathetic nervous system, in laboratory animals. To date, though, the use of dexmedetomidine to treat substance withdrawal in the clinical arena remains anecdotal (Table 1).[3-6,21] Our current cohort of seven patients is the largest series to date regarding the use of dexmedetomidine to control withdrawal behavior in the ICU population. We postulated

Table 1. Anecdotal reports of dexmedetomidine to control withdrawal in the ICU

Author	Patient demographics	Dexmedetomidine dosing regimen
Maccioli GA[3]	The first patient was a 49-year-old woman with a history of alcohol and cocaine use who presented with severe agitation.	Dexmedetomidine was administered as a loading dose of 1 μg/kg over 20 minutes, followed by an infusion of 0.7 μg/kg/hr. The dexmedetomidine was continued for 36 hours and effectively controlled the patient's agitation and autonomic hyperactivity.
	The second patient was a 54-year-old man who was recovering from multiple-system organ failure and a six-week ICU course, during which time he had received large doses of opioids and benzodiazepines.	Dexmedetomidine, administered as a bolus of 1 μg/kg followed by an infusion of 0.7 μg/kg/hr, effectively controlled the withdrawal behavior. Dexmedetomidine was weaned over a seven-day period.
Multz AS[4]	Thirty-three-year-old with a history of multiple substance abuse (cocaine, ketamine, cannabinoids, and benzodiazepines) with septic shock and multiple-system organ failure, which required prolonged mechanical ventilation and sedation with benzodiazepines, propofol, and opioids. Withdrawal behavior (tachypnea, fever, tachycardia) developed despite propofol (50 μg/kg/min) and a fentanyl patch.	Dexmedetomidine was started at 0.7 μg/kg/hr without a loading dose. The use of dexmedetomidine allowed for the tapering and discontinuation of the other medications. The dexmedetomidine was continued for a total of five days and then was weaned over a 48-hour period.
Finkel JC, Elrefai A[5]	Eight-month-old infant with Hurler syndrome who had required prolonged sedation during mechanical ventilation. The patient had undergone tracheostomy, and the goal was to discontinue use of benzodiazepines and opioids. Using a Bispectral Index monitor, the authors titrated the dexmedetomidine infusion after the midazolam and fentanyl infusions were discontinued.	Dexmedetomidine in a dose of 0.2 to 0.7 μg/kg/hr for seven days and then tapered over a 24-hour period allowed for withdrawal of benzodiazepines and opioids.
Baddigam K et al.[6]	Seventeen-year-old with infected aortic valve. History of cannabinoid, tobacco, ethanol, and other substance abuse. Manifested withdrawal symptoms during postoperative period.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr, effectively controlled withdrawal behavior (diaphoresis, agitation, tachycardia, and hypertension).
	Four-month-old infant exhibiting withdrawal behavior after use of fentanyl for sedation during mechanical ventilation following repair of congenital heart disease.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr, effectively controlled the withdrawal behavior. Infusion weaned over 48 to 72 hours.
	Fifty-five-day-old infant exhibiting withdrawal behavior after the use of fentanyl for sedation during mechanical ventilation following palliation of congenital heart disease.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/hr, effectively controlled the withdrawal behavior.
Finkel et al.[21]	Two pediatric patients (six-month-old and seven-year-old) who exhibited withdrawal behavior related to the prolonged administration of opioids and benzodiazepines following cardiac transplantation.	Dexmedetomidine, administered as a loading dose of 1 μg/kg followed by an infusion of 0.8 to 1.0 μg/kg/hr, effectively controlled the withdrawal behavior. Dexmedetomidine infusions administered and then weaned for a total duration of use of eight and 16 days in the two patients, respectively.

that dexmedetomidine was a viable option in such patients for several reasons: 1) both animal studies and anecdotal clinical reports have demonstrated its efficacy in treating withdrawal; 2) when compared to clonidine, dexmedetomidine has a shorter half-life, thereby allowing for ease of titration when administered by continuous infusion and adjustments as needed to control withdrawal behavior; 3) there is increasing experience with the use of dexmedetomidine in various clinical scenarios in the pediatric population; 4) dexmedetomidine has been shown to have limited effects on respiratory function, which is helpful when trying to control withdrawal behavior in patients like those in the current series who have recently been extubated; and 5) dexmedetomidine effectively controls withdrawal behaviors regardless of the withdrawn agent in question. Although the majority of our patients' issues were likely related to opioids, they were all also receiving frequent intermittent doses of benzodiazepines. In such instances, it is clinically useful to have a single agent that can be used when withdrawal may be related to more than one drug or medication.

Dexmedetomidine can have deleterious effects on both hemodynamic and respiratory function. Using CO_2 response curves, Belleville et al.[22] reported a slope depression of the CO_2 response curve and a decrease in minute ventilation at an end-tidal concentration ($ETCO_2$) of 55 mmHg following a bolus dose of 2 μg/kg. Hemodynamic effects have included hypotension, hypertension, and bradycardia, which occur most commonly with the loading dose.[23-25] Although in most cases such problems have been clinically insignificant, given the potential impact on the critically ill ICU patient the use of dexmedetomidine mandates close monitoring of hemodynamic and respiratory function.

α_2-adrenergic agonists have been shown to be effective in the treatment of withdrawal from various substances, including cannabinoids, alcohol, benzodiazepines, and opioids. The current cohort of patients adds to the increasing number of patients reported on in the literature in whom dexmedetomidine has been used to successfully treat drug and medication withdrawal. Our dosing regimen included an initial bolus dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr. Repeat of the bolus dose and an increase of the infusion were required in two patients who had received larger doses of fentanyl. In our cohort, the dexmedetomidine infusion was decreased in increments of 0.1 μg/kg/hr every 12 to 24 hours.

Drawbacks of the current study include the use of the Finnegan score for a non-neonatal population and the study's retrospective design. Due to the lack of other withdrawal scores, our practice has been to use the Finnegan score not necessarily to define the severity of withdrawal but, more importantly, to provide an easy checklist to identify withdrawal behaviors and, by repeated monitoring over time, to attempt to gauge the efficacy of therapeutic interventions. Although retrospective, we hope that these preliminary data will provide the impetus for the performance of prospective clinical trials. Ideally, such trials would acquire data that we were unable to obtain in our retrospective study, such as the specific withdrawal symptoms present in each individual and which symptoms were most improved by treatment. It would also be practical to explore whether variations in age or individual opioid/benzodiazepine doses had any impact on the treatment's effectiveness. Questions to be answered may include whether dexmedetomidine should be used to treat withdrawal once it occurs or whether it has a role as a prophylactic agent in high-risk patients. Although our cohort was sedated with a fentanyl infusion, all patients also received intermittent doses of midazolam for supplemental sedation; it would be helpful to determine the efficacy of dexmedetomidine in treating/preventing withdrawal in various pharmacologic regimens for sedation involving opioids, benzodiazepines, and barbiturates, and perhaps even propofol-based regimens. More information is also needed to determine the appropriate dosing regimens and effective weaning patterns.

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