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 α2-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 non-parametric data (Finnegan scores) are presented as the
median and range. A nonpaired t-test was used to com-
pare the maximum fentanyl-infusion rate in patients
who required a repeat bolus dose of dexmedetomidine
and an increase in the infusion rate to control withdraw-
al 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 mida-
zolam for sedation, during mechanical ventilation for
respiratory failure due either to a primary pulmonary
infection or following surgery for congenital heart dis-
ease. The patients were breathing spontaneously, hav-
ing 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 max-
imum 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 dis-
continued 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 adminis-
tered 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 signifi-
cant 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 dexmedeto-
midine. The dexmedetomidine infusion was decreased
in increments of 0.1 µg/kg/hr every 12 to 24 hours. No re-
bound hypertension was seen with this weaning regimen.

DISCUSSION

Dexmedetomidine is an α₂-adrenergic agonist. Al-
though both dexmedetomidine and clonidine possess
specificity for the α₂ versus the α₁ receptor, the specifici-
ty 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 ani-
mal studies have reported the successful use of cloni-
dine to treat withdrawal from various agents, including
opioids, cannabinoids, and ethanol.9-16 Baumgartner
and Rowen9 randomly assigned 50 adults undergoing
ethanol withdrawal to receive either transdermal cloni-
dine or chlorodiazepoxide. Therapy was deemed effect-
ive 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.19 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, per-
formed using spinal anesthesia. The patients were ran-
donized 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, mani-
festing as hyperactivity of the sympathetic nervous sys-
tem, in laboratory animals. To date, though, the use of
dexmedetomidine to treat substance withdrawal in the
clinical arena remains anecdotal (Table I).3,6,21 Our cur-
rent cohort of seven patients is the largest series to date
regarding the use of dexmedetomidine to control with-
drawal behavior in the ICU population. We postulated
Table 1. Anecdotal reports of dexmedetomidine to control withdrawal in the ICU

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient demographics</th>
<th>Dexmedetomidine dosing regimen</th>
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<tbody>
<tr>
<td>Maccioli GA³</td>
<td>The first patient was a 49-year-old woman with a history of alcohol and cocaine use who presented with severe agitation.</td>
<td>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. 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.</td>
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<td>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.</td>
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<td>Multz AS⁴</td>
<td>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.</td>
<td>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.</td>
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<td>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.</td>
<td>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.</td>
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<tr>
<td>Finkel JC, Elrefai A¹</td>
<td>Seventeen-year-old with infected aortic valve. History of cannabinoid, tobacco, ethanol, and other substance abuse. Manifested withdrawal symptoms during postoperative period. Four-month-old infant exhibiting withdrawal behavior after use of fentanyl for sedation during mechanical ventilation following repair of congenital heart disease. Fifty-five-day-old infant exhibiting withdrawal behavior after the use of fentanyl for sedation during mechanical ventilation following palliation of congenital heart disease.</td>
<td>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). 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. 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.</td>
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<td></td>
<td>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.</td>
<td>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.</td>
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</table>
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 CO₂ response curves, Belleville et al. reported a slope depression of the CO₂ response curve and a decrease in minute ventilation at an end-tidal concentration (ETCO₂) 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. 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.

α₂-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 which 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.

REFERENCES


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