

Dexmedetomidine for Sedation during Withdrawal of Support

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ABSTRACT: Agents used to control end-of-life suffering are associated with troublesome side effects. The use of dexmedetomidine for sedation during withdrawal of support in pediatrics is not yet described. An adolescent female with progressive and irreversible pulmonary deterioration was admitted. Despite weeks of therapy, she did not tolerate weaning of supplemental oxygen or continuous bilevel positive airway pressure. Given her condition and the perception that she was suffering, the family requested withdrawal of support. Despite opioids and benzodiazepines, she appeared to be uncomfortable after support was withdrawn. Ketamine was initiated. Relief from ketamine was brief, and its use was associated with a "wide-eyed" look that was distressing to the family. Ketamine was discontinued and a dexmedetomidine infusion was initiated. The patient's level of comfort improved greatly. The child died peacefully 24 hours after initiating dexmedetomidine from her underlying disease rather than the effects of the sedative.

KEYWORDS: palliative care, hypnotics and sedatives, dexmedetomidine, lung disease

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Background

Opioids, benzodiazepines,¹ ketamine, propofol,² barbiturates,³ and neuroleptics are agents utilized to provide sedation to manage refractory pain and symptoms at the end of life. A recent retrospective analysis based on data from the Pediatric Health Information System and Premier Perspective Database between 2007 and 2011 confirmed this, and also noted an increasing use of dexmedetomidine. While patients receiving palliative sedation have been shown to survive longer than matched untreated cohorts,⁴ and opioids and benzodiazepines may prolong survival after withdrawal of support,⁵ the pharmacologic therapies used in these situations are associated with adverse effects. These include impaired communication,⁶ hypersalivation, respiratory depression, delirium, myoclonus, propylene glycol toxicity, and upper airway obstruction. The side effects of these agents may inhibit or delay a practitioner's prescription⁷ or a family's acceptance of their use.⁸ Moreover, families experience distress because their desire for continued interaction is often compromised by the agents used to treat end-of-life suffering.⁹

Dexmedetomidine, a highly selective α_2 agonist, is being used with increasing frequency in pediatric patients for sedation.¹⁰ It has adverse effects which are known. It is a potent sedative that induces a state of non-Rapid Eye Movement (REM)-like sleep¹¹ from which patients may be easily aroused rather than frank unconsciousness. It does not suppress the respiratory drive,¹² and it has a wide range of

useful actions, including sialoschisis, anxiolysis,¹³ analgesia,¹⁴ as well as prevention of recall.¹⁵ All of this would suggest that dexmedetomidine may be a very useful medication in the setting of palliative sedation or withdrawal of support. However, the literature regarding its use in palliative care is sparse.^{3,16,17}

Case Description

An adolescent female with severe developmental delay, spastic quadriplegia, obstructive sleep apnea, cortical blindness, scoliosis, renal disease, bilateral hip dislocation, chronic lung disease, and a seizure disorder was admitted for respiratory distress and worsening chronic respiratory failure. This was her sixth admission in a year, four of which were secondary to respiratory failure. Her need for respiratory support had progressively increased and now included nocturnal bilevel positive airway pressure (BiPAP) support, which frequently was used for 24 hours a day secondary to oxygen desaturations. Moreover, her ability to interact had declined to the point where she was now non-interactive except for her facial expressions, which her family perceived to indicate that she was suffering and in pain. Despite three weeks of aggressive pulmonary therapy, she was not able to tolerate weaning of supplemental oxygen or continuous BiPAP support. With no acute interceding illness, her lung disease was considered to be the result of a chronic, progressive, and irreversible process, which would ultimately result in her death. A multi-disciplinary meeting was convened during which all potential



treatment options were presented to the family. Her resuscitation status had been established previously as “Do Not Attempt Resuscitation/Do Not Intubate” during previous admissions. Given her progressive, irreversible pulmonary deterioration, the perception that she was suffering, and her declining level of interaction, the family opted to not pursue any additional life-sustaining therapies (eg, tracheostomy, spinal fusion) and requested withdrawal of BiPAP support. All members of the medical team concurred with what was seen as a reasonable request.

At the time of withdrawal, she was receiving scheduled enteral lorazepam and morphine with additional morphine doses as needed. When the BiPAP was removed, the patient was placed on a high-flow oxygen mask, and she initially appeared quite comfortable. Over time, however, she became increasingly tachypneic, and all concurred that additional treatment was needed. Consequently, intravenous ketamine (0.5 mg/kg) and midazolam (0.05 mg/kg) were added to her treatment regimen to achieve a level of sedation that would provide comfort. Although this therapy appeared to provide comfort, it was associated with a “wide-eyed” look, which was troubling to the family who perceived this as an indication of distress. Moreover, any benefit from the ketamine was short-lived, and her initial level of perceived discomfort promptly recurred. Consequently, the child received a dose of fentanyl (0.5 µg/kg) and a decision was made to begin dexmedetomidine. The initial rate of dexmedetomidine was 0.2 µg/kg/hour, and this was titrated to 0.4 µg/kg/hour. No bolus was administered. With these interventions, she appeared to be quite comfortable and remained so for 14 hours. At that point, she displayed increased work of breathing and was given a single breakthrough dose of enteral morphine (0.05 mg/kg). With this intervention, she remained comfortable for nearly four hours, at which point, she again appeared slightly uncomfortable. She received midazolam (0.05 mg/kg) intravenously, and the infusion rate of dexmedetomidine was increased to 0.7 µg/kg/hour. Approximately ten hours later, the patient died seemingly comfortable with no additional signs of distress.

Discussion

Dexmedetomidine would appear to hold great potential for use in end-of-life care. It is a potent sedative that also possesses analgesic and opioid sparing properties.¹⁸ Its sedative effects induce a state of non-REM like sleep fostering easy awakening if desired. It causes dose-dependent amnesia¹⁹ and may reduce the likelihood of delirium in comparison to benzodiazepines.²⁰ Moreover, it is reported to possess anxiolytic¹³ and antisialagogue properties.²¹ Each of these effects further suggests that it may be a useful medication in the setting of palliative sedation or sedation used during withdrawal of support.

Despite these purported benefits, potential side effects must be considered before dexmedetomidine is used as primary therapy in palliative sedation. For example, dexmedetomidine

exhibits pro-arrhythmogenic properties, specifically bradycardia;²² there are reports of bradycardia-related death in patients being treated with dexmedetomidine.^{23,24} Additional cardiovascular complications include asystole,²⁵ pacemaker noncapture,²⁶ brief sinus pause,²⁷ prolongation of the QT²⁸ and PR intervals,²⁹ and sinus arrest.^{30,31} While dexmedetomidine use has been associated with hypotension,³² particularly in relation to loading doses,³¹ Ebert et al demonstrated that higher doses may lead to increased blood pressure, but decreased cardiac output.¹⁹ Despite these potential adverse cardiovascular effects, dexmedetomidine has been widely used as a sedative in infants and children with congenital heart disease.^{33,34} Moreover, it has been used during the perioperative period of congenital cardiac surgery to treat atrial and junctional tachyarrhythmias.³⁵

Other factors may also temper the use of dexmedetomidine in palliative care. It is metabolized by the liver, and thus may be less safe in patients with hepatic insufficiency. It is almost exclusively cleared (95%) by the kidneys, and renal dosing adjustment has been suggested by some to avoid excessive sedation.³⁶ Further, drug-induced adrenal insufficiency has been reported;³⁷ however, data suggest that, at normal doses, this effect is related to abnormal adrenocorticotrophic hormone (ACTH) stimulation and not steroidogenesis inhibition.³⁸ Additionally, although the short-term benefits of dexmedetomidine are becoming more established, the safety of its long-term use of has not been studied as extensively. Case reports and retrospective analyses suggest that infusions used for days to weeks are, in most cases, relatively safe and well tolerated.^{33,39–41} Although not consistently reported, withdrawal and tachyphylaxis for infusions lasting >24 hours have been described.⁴²

Despite these concerns and potential adverse effects, dexmedetomidine appears to offer some advantages when compared to other medications used in palliative sedation. In contrast to ketamine and its dissociative state, dexmedetomidine allows patients to be easily awakened. Depending on the degree of sedation, patients can awaken, interact with caregivers, and engage in complex cognitive tasks.^{43,44} Agents such as midazolam and propofol may require a dosing change to allow interaction. While not as effective as benzodiazepines, dexmedetomidine inhibits recall in a dose-dependent fashion.^{15,19} Unlike pentobarbital and benzodiazepines, dexmedetomidine has analgesic properties. Moreover, it has multiple administration advantages over propofol. Propofol causes pain on injection,⁴⁵ whereas dexmedetomidine does not,³¹ and dexmedetomidine may be administered subcutaneously,⁴⁶ broadening the scope of where it may be administered. Propofol also has variable compatibility with metoclopramide, midazolam, diazepam, and morphine⁴⁷—medications compatible with dexmedetomidine and commonly used in end-of-life care. Finally, the limited effects of dexmedetomidine on respiratory drive, combined with its lack of effect on upper airway patency,⁴⁸ may make it safer than propofol, benzodiazepines, and opioids in end-of-life care.

Conclusion

This report is the first to describe the use of dexmedetomidine for sedation used in the withdrawal of support in a pediatric patient. Patients who suffer from illnesses that are neither amenable to curative therapy nor effective symptom control are faced with immense suffering. The use of a sedative agent that induces a sleep-like state allowing rapid awakening, provides analgesia, alleviates anxiety, decreases oral secretions, does not suppress the respiratory drive, affect the airway, or induce delirium would appear to be an ideal medication for palliative sedation when life sustaining therapy for these individuals is withdrawn. Its compatibility with other medications used in end-of-life care may prove practical. Its use in sedation for withdrawal of support or palliation of intolerable suffering would appear to merit further prospective study.

Author Contributions

Conceived and designed the experiments: RT and GC. Wrote the first draft of the manuscript: CO, RT, and GC. Contributed to the writing of the manuscript: CO, RT, and GC. Agreed with manuscript results and conclusions: CO, RT, and GC. Jointly developed the structure and arguments for the paper: CO, RT, and GC. Made critical revisions and approved the final version: CO, RT, and GC. All the authors reviewed and approved the final manuscript.

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