Prolonged Dexmedetomidine Infusion as an Adjunct in Treating Sedation-Induced Withdrawal

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The patient was a multiple-substance abuser admitted to the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS), subsequently complicated by ventilator-associated pneumonia (VAP). He required long-term sedation with multiple drugs with potential addiction and withdrawal complications. We started dexmedetomidine IV after we were unable to wean him from mechanical ventilation. Over 7 days on dexmedetomidine, he was successfully weaned from the ventilator, lorazepam, and IV fentanyl without withdrawal symptoms, adverse events, or sequelae.

Case Report

A 33-yr-old man with a history of substance abuse with cocaine, ketamine, marijuana, and benzodiazepines presented to the emergency department with recent-onset shortness of breath and pleuritic chest pain. Before arrival, he had used an unknown quantity of intranasal ketamine. He was febrile (38.3°C), was hypotensive with a blood pressure of 77/52 mm Hg, and had a heart rate of 146 bpm, a respiratory rate of 22 breaths/min, and an oxygen saturation of 87% on 100% oxygen. Lung examination revealed coarse bilateral breath sounds with crackles. Cardiac examination revealed tachycardia that was regular with no murmurs, rubs, or gallops. The rest of his physical examination was unremarkable.

The patient was very agitated and had to be sedated and restrained. A chest radiograph showed bilateral alveolar infiltrates encompassing the entire field in both lungs. An endotracheal tube was introduced, and he was sedated with propofol (30 µg · kg⁻¹ · min⁻¹) and lorazepam (2 mg/h).

He remained persistently hypotensive and was started empirically on broad-spectrum antibiotics for possible septic shock. An echocardiogram showed global ventricular dysfunction. A right heart catheter subsequently revealed a pulmonary capillary wedge pressure of 24 mm Hg with a cardiac output of 2.1 L/min. Inotropic therapy significantly improved his hemodynamic profile.

A repeat echocardiogram showed normalization of biventricular function. There was no improvement in his chest radiograph or oxygenation status, and his clinical picture was consistent with ARDS. He maintained an oxygen saturation of 89% on 100% oxygen with positive end-expiratory pressure (PEEP) to 15 cm H₂O. He was then paralyzed with cisatracurium. Lorazepam and propofol were continued, and fentanyl (100 µg/h) was added.

His ICU course was complicated by an episode of VAP with Acinetobacter baumannii. Mechanical ventilation could not be discontinued because of persistently large oxygen requirements. On Day 17, a tracheostomy was performed. On Day 18, methylprednisolone was started at 2 mg/kg.

His oxygenation status slowly improved, and by Day 21 he was maintained on 40% oxygen with a PEEP of 5 cm H₂O. Cisatracurium was discontinued, but he remained tachycardic and febrile. At this point, he was still being maintained on lorazepam, propofol, and fentanyl. In an attempt to taper the lorazepam and fentanyl, haloperidol was added at 20 mg every 4 h. Despite propofol doses in the range of 50 µg · kg⁻¹ · min⁻¹ and a fentanyl patch (25 µg), attempts at weaning from lorazepam or fentanyl resulted in persistent fevers, tachycardia, and tachypnea.

On Day 25, an IV infusion of dexmedetomidine was started at 0.7 µg · kg⁻¹ · h⁻¹ without a bolus dose. This medication was chosen with the hope that the α₂-adrenoceptor agonist effects would help with symptoms related to withdrawal from opioids and benzodiazepines. With the combination of dexmedetomidine and the fentanyl patch, we discontinued the lorazepam and IV fentanyl. On Day 28 (Day 3 of dexmedetomidine), we began to taper haloperidol. On Day 4, dexmedetomidine was decreased to 0.5 µg · kg⁻¹ · h⁻¹. The patient awoke and was alert, oriented, and cooperative. While still receiving dexmedetomidine, he was successfully weaned from the ventilator. On Day 6, dexmedetomidine was decreased to 0.2 µg · kg⁻¹ · h⁻¹; on Day 7, it was stopped. No hemodynamic sequelae were observed during the entire time of dexmedetomidine infusion. The patient was eventually weaned from the fentanyl patch, angiocatheters were removed, and he was transferred to a rehabilitation facility.

Discussion

One of the problems encountered when treating ARDS in a patient already addicted to narcotics and benzodiazepines is the withdrawal process itself. For the patient to tolerate the endotracheal tube for extended periods, he or she must be kept sedated and...
comfortable. For critically ill patients, lorazepam is the preferred drug for prolonged treatment of anxiety, and fentanyl is recommended for acutely distressed patients with hemodynamic instability (1). Unfortunately, the drugs of choice for this patient’s therapy were similar to his drugs of abuse. When his respiratory condition had improved sufficiently that ventilator assistance was no longer medically necessary, benzodiazepine and opioid withdrawal became the limiting factor in his recovery. Propofol did not allay his anxiety or control the withdrawal symptoms.

Hypertension, anxiety, agitation, tachycardia, and fever occurring during benzodiazepine and opioid withdrawal are attenuated by the $\alpha_2$ agonists (2–4). Withdrawal from narcotics is characterized by a hypernoradrenergic state. The $\alpha_2$-adrenoceptor agonists decrease sympathetic outflow and noradrenergic activity, counteracting the physiologic effects of withdrawal rather than acting as a substitute for the drug being withdrawn (5). These effects are largely mediated by the postsynaptic $\alpha_{2A}$ receptor subtype in the locus coeruleus (6–8). Reduced sympathetic tone and increased parasympathetic tone reduce metabolism, heart rate, myocardial contractility, and vascular resistance. These effects reduce myocardial oxygen requirements (9). Clonidine has been used to attenuate the symptoms of withdrawal from narcotics and naloxone-induced hypertension for more than 20 years (10–12). Dexmedetomidine has a higher affinity for the $\alpha_{2A}$ receptors than clonidine, resulting in more selective $\alpha_{2A}$ activation and less of the deleterious $\alpha_1$ stimulation (13).

Opiates and $\alpha_2$ agonists act synergistically on central sympathetic outflow (14). The potentiating effects of the $\alpha_2$ agonists on morphine reduce the amount of opioid needed and how long a fixed dose of the opioid is effective (15). The mechanism by which dexmedetomidine enhances the analgesic effects of morphine is not clear. There is some evidence that $\alpha_2$ agonist-induced antinociception results from acetylcholine release inhibiting nociceptive neurons in the spinal cord (9).

A major advantage of dexmedetomidine over other sedatives is respiratory stability (16,17). A patient can be maintained at a Ramsay sedation level of 2–4 on a continuous infusion during weaning and extubation without depression of the respiratory drive. The characteristic effects of dexmedetomidine relieve anxiety, reduce opioid needs, and facilitate conscious sedation (9). Dexmedetomidine also blunts the effects of cocaine (4). In this case, dexmedetomidine attenuated the symptoms of withdrawal, allowing a smooth transition off the ventilator and the lorazepam and fentanyl infusions.

Two clinical studies were recently published in which dexmedetomidine was used for up to seven days in the medical ICU (18,19). Hemodynamic stability was preserved, with no myocardial depression and no rebound effect on withdrawal.

In the case described here, dexmedetomidine facilitated withdrawal from lorazepam and fentanyl. With no risk of respiratory depression, conscious sedation was maintained throughout weaning and extubation. The symptoms of withdrawal were relieved without delaying weaning.

References