

Weaning from prolonged mechanical ventilation using an antipsychotic agent in a patient with acute stress disorder

Lisa J. Rosenthal, MD; Victor Kim, MD; Deborah R. Kim, MD

Objective: To report the use of a second-generation antipsychotic agent to assist weaning from prolonged mechanical ventilation in an anxious patient.

Design: Case report.

Setting: Medical intensive care unit at the Hospital of the University of Pennsylvania.

Patient: A 39-yr-old white female whose severe anxiety prohibited weaning from prolonged mechanical ventilation.

Interventions: Initiation of quetiapine as treatment for severe anxiety that was unresponsive to sedative hypnotics.

Measurements and Main Results: Once a therapeutic dose of quetiapine was reached, ventilator support was removed within 24 hrs.

Conclusions: A second-generation antipsychotic agent was successfully used to facilitate weaning in a very anxious patient, possibly secondary to anxiolysis or direct effect on respiratory drive. Further investigations of pharmacologic intervention should be done to inform practice guidelines in difficult-to-wean patients suffering from severe anxiety. (*Crit Care Med* 2007; 35:2417–2419)

KEY WORDS: mechanical ventilation; ventilator weaning; anxiety disorder; posttraumatic stress disorder; stress disorders, traumatic, acute; antipsychotic agents

Weaning from mechanical ventilation is reported by many patients to be a physically and emotionally uncomfortable experience. Those patients with comorbid anxiety disorders may be particularly vulnerable to difficulties with weaning. Prolonged mechanical ventilation is associated with numerous medical complications as well as increased occupation of intensive care beds, resource consumption, and costs; it is therefore crucial that psychiatric barriers to weaning be addressed in the comprehensive care plan for difficult-to-wean patients (1–3).

The evidence for using psychotropic medications in this population is extremely limited (4, 5). Although psychiatric comorbidities are considered to be risk factors for ventilator dependency, no studies have been conducted and no expert recommendations are provided for pharmacologic anxiolysis during weaning (6). The use of

benzodiazepines seems to be common practice, but it is not effective for all patients. We present a case report of facilitated ventilator weaning using quetiapine, a second-generation antipsychotic agent.

CASE REPORT

This case report did not require Institutional Review Board (IRB) review per the University of Pennsylvania IRB protocol. The IRB was contacted regarding the inclusion of an author (VK) from another institution and granted permission that he be given access to patient medical data without identifying information.

The patient was a 39-yr-old white female with a history of multiple myeloma, deep venous thrombosis and pulmonary embolism status post vena caval filter, and adjustment disorder with depressed mood who underwent an autologous bone marrow transplant. Four days after induction therapy the patient developed neutropenic fever, and 2 days later the patient was intubated for acute hypoxemic respiratory failure secondary to enterococcus pneumonia and staphylococcal bacteremia. The patient was maintained on volume cycled ventilation. Septic shock developed despite several days of broad-spectrum antibiotics, requiring aggressive volume resuscitation and vasopressor support.

The patient underwent tracheostomy and percutaneous gastrostomy after 3 wks of pro-

longed mechanical ventilation. After extended courses of antibiotics, the patient defervesced, hypotension resolved, and gas exchange improved, with a P_{aO_2}/F_{iO_2} ratio of 240. Aggressive diuresis was performed because of significant peripheral edema. Out-patient medications were restarted, including escitalopram for depression and metoprolol for hypertension. A spontaneous breathing trial was initiated, but the patient became immediately tachypneic and was placed back on volume cycled ventilation. Pressure support ventilation was initiated as a weaning method. The patient was gradually weaned over several days to minimal pressure support (pressure support ventilation, 3 mm Hg) with no patient discomfort and appropriate physiologic variables to discontinue mechanical ventilation. Spontaneous breathing trials were reinitiated; the patient tolerated gradual increases in duration of independent ventilation, with acceptable gas exchange, hemodynamics, tidal volume, and respiratory rate. While she was undergoing mechanical ventilation, low-level pressure support ventilation was used, producing a respiratory rate of 10–14 with tidal volumes of approximately 400 mL. However, she was never able to tolerate >1 hr off mechanical ventilation, with no identifiable cardiac, pulmonary, or infectious cause. This phenomenon was attributed to anxiety. The intensive care unit team continued her es-

From the University of Pennsylvania Department of Psychiatry, Philadelphia, PA (LJR, DRK); and Temple University School of Medicine, Division of Pulmonary and Critical Care Medicine, Philadelphia, PA (VK).

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For information regarding this article, E-mail: lisa.rosenthal@uphs.upenn.edu

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escitalopram and metoprolol, started clonazepam, and administered as needed doses of lorazepam before weaning trials, but the patient reported no relief.

After 3 wks of unsuccessful weaning attempts, the psychosomatic consultation service was consulted to aid in the management of anxiety, which was believed by the medical intensive care unit (MICU) team to prohibit weaning from mechanical ventilation. The patient reported extreme anxiety during spontaneous breathing trials; she became tachypneic, tachycardic, and diaphoretic and begged staff and family to restart mechanical ventilation. She was inconsolable at these times and neither trusted bedside monitors nor accepted reassurances from staff and family that she was breathing independently. Her level of distress prevented implementation of relaxation techniques, and she was convinced that the sensation of dyspnea signaled impending death. Additional fears included dying while asleep, even during ventilator assistance. She endorsed multiple symptoms on the Acute Stress Disorder Scale (7), including feelings of unreality, nightmares, intrusive thoughts, and hyperarousal, all of which were focused on the experience of respiratory failure.

Psychiatric recommendations included increasing the escitalopram dose and initiating quetiapine 50 mg in the morning, 50 mg at noon, and 100 mg at night. Initially the patient denied any relief of anxiety, but her family and the MICU team reported a lower level of anxiety exemplified by fewer requests for assisted ventilation. Quetiapine was increased to 100 mg every 8 hrs after 3 days, and nursing staff reported immediate symptomatic improvement. Within a day, the patient was able to maintain spontaneous breathing and became ventilator independent. She continued to express anxiety and a belief that she would stop breathing; however, requests for reinitiation of mechanical ventilation ceased. Her QTc was not affected by the addition of quetiapine. She was subsequently discharged to a long-term rehabilitation facility.

DISCUSSION

Qualitative descriptions of patient experience during weaning from ventilation include frustration, uncertainty, hopelessness, fear, and lack of mastery (8). Anxiety can be associated with many medical disorders, particularly respiratory disease, but many patients find ventilator weaning to be especially anxiety provoking. Generally, with reassurance about medical stability

and clinical improvement, anxiety wanes over time. In this patient, the MICU team ruled out any medical etiology causing failure to wean and determined that anxiety was the primary barrier to successful weaning attempts. The differential diagnosis of anxiety in this patient includes panic disorder, adjustment disorder with anxious mood, delirium, anxiety secondary to a medical condition, and acute stress disorder.

Panic attacks are characterized by discrete episodes of overwhelming fear, a sense of loss of control, and physical symptoms of hyperarousal such as difficulty breathing, diaphoresis, and tremor. Panic attacks are typically short-lived, peaking in intensity within 10 mins of onset. Panic disorder is defined by panic attacks that occur repeatedly and spontaneously. This patient did not experience spontaneous panic attacks, and although her anxiety did vary in intensity over time, she was never anxiety free.

The diagnosis of adjustment disorder with anxiety is made when a patient experiences anxiety that is overwhelming and out of proportion to the stressor. Once the stressor is removed, the anxiety improves. However, patients who meet the strict criteria for more severe anxiety syndromes no longer qualify for the diagnosis of adjustment disorder, even if their symptoms are precipitated by a stressor.

Delirium also was considered in this case. The patient was too anxious to complete a detailed survey of her cognitive function, so it is possible that delirium influenced her beliefs about weaning. However, she demonstrated that she was fully oriented, addressed questions appropriately, and nursing staff denied waxing and waning confusion or periods of altered consciousness. In addition, the MICU team did not find any medical pathology that could explain her anxiety, making anxiety secondary to a medical condition unlikely.

Most likely this patient's anxiety was a reaction to the trauma of severe illness and the experience of respiratory failure. Along with the experience of a life-threatening event, the diagnosis of acute stress disorder (ASD) includes dissociative symptoms, such as numbness or detachment, derealization, depersonalization, or dissociative amnesia, avoidance, and hyperarousal, which occur within 2 days to 4 wks of the stressor (9). Our patient had experienced a life-threatening medical emergency and endorsed most of the symptomatic criterion for ASD. ASD is an early response to a traumatic event,

whereas posttraumatic stress disorder develops later with or without a previous diagnosis of ASD. There is a growing body of literature reporting ASD and posttraumatic stress disorder following intensive care treatment (10, 11).

The patient's belief that she would die off the ventilator could be described as a fixed, false belief, or a delusion. However, her fears were based on past experience and therefore were not necessarily irrational. In this case, her belief is better conceptualized as an overvalued idea and a manifestation of anxiety. Extreme, irrational fear is common in severe anxiety and has been described in patients who have been exposed to traumatic events.

Medical and nursing guidelines stress the importance of addressing psychological factors during weaning (6). Unfortunately, there are no published trials of pharmacotherapy for difficult-to-wean patients with anxiety. Current published research on treatments for psychological suffering during ventilator weaning includes investigations of hypnosis and biofeedback (12). One study on biofeedback showed a decrease in the duration of mechanical ventilation (13). A case report of a patient with severe anxiety and posttraumatic symptoms from multiple life-threatening medical crises reported successful weaning using hypnosis techniques (14). In the circumstances of this case, the patient was so anxious that she was unable to focus on relaxation imagery, and she was not reassured by cardiac and respiratory monitors demonstrating normal hemodynamics and oxygenation during weaning trials.

Despite therapeutic doses of benzodiazepines, the patient's anxiety prevented implementation of appropriate and necessary medical treatments. Increasing the escitalopram dose would not have been immediately helpful, so a second-generation antipsychotic agent was considered. Second-generation antipsychotic agents are thought to be different from first-generation antipsychotic agents, such as haloperidol, because of their affinity for serotonergic receptors and faster rates of dissociation from dopamine receptors. In addition, they are less likely to induce extrapyramidal symptoms or hyperprolactinemia. Quetiapine is an antagonist at multiple neurotransmitter receptors including serotonin 5-HT_{1A} and 5-HT₂, dopamine D₁ and D₂, histamine H₁, and adrenergic α ₁- and α ₂-receptors. It does not demonstrate affinity for muscarinic or benzodiazepine receptors. There are some data supporting the use of second-

generation antipsychotic agents for anxiety disorders as adjunctive pharmacotherapy (15–17). Second-generation antipsychotic agents should be used with caution in the elderly demented population due to the increased risk of death from cardiac and respiratory complications.

The diagnosis of ASD provides a possible explanation for this patient's limited response to benzodiazepines; ASD and posttraumatic stress disorder are thought to be less responsive to sedative-hypnotics than other anxiety disorders (18). Alternatively, her improvement may have been due to resolution of her belief that she would stop breathing if not mechanically ventilated. Her communication was limited by tracheostomy, but she endorsed this idea "100%" when questioned. The addition of an antipsychotic agent may have provided benefit as a treatment for psychosis; however, this conviction remained following weaning. The benefit from quetiapine seemed to be secondary to anxiolysis and not related to resolution of her beliefs about independent ventilation.

A possible physiologic mechanism for improvement with quetiapine might include the effect of peripheral and central D2 blockade on respiratory drive. Administration of low-dose dopamine in healthy volunteers decreases the autonomic response to hypoxia through D2 receptors in the carotid body (19). Consequently, dopamine should be used with caution in patients weaning from mechanical ventilation. Pedersen et al. (20) demonstrated that administering haloperidol to eucapnic, healthy volunteers could increase acute ventilatory response to hypoxia. It is possible that the addition of quetiapine increased this patient's ventilatory drive, but whether it affected her subjective sense of dyspnea is unknown. It is also unclear whether dopamine antagonism of ventilatory drive is clinically relevant to the circumstances of this case.

Anxiety can be caused or exacerbated by a number of factors present in an intensive care setting such as medications, sleep

deprivation, and psychological stress resulting from coping with severe medical illness. It is important to consider these systemic and environmental issues when diagnosing an anxiety disorder in the intensive care unit and to address them before initiating pharmacotherapy for anxiety. This case illustrates use of a second-generation antipsychotic agent to facilitate weaning in a patient with acute stress disorder. Anxious patients on prolonged mechanical ventilation whose symptoms are unresponsive to sedative hypnotics may benefit from short-term treatment with quetiapine.

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