Dexmedetomidine for Acute Alcohol Withdrawal
Jessica Traeger, PharmD; Andreea Popa, PharmD, BCPS; Jason Makii, PharmD, BCPS

The estimated prevalence of alcohol abuse among hospitalized inpatients is 20%, and 10% to 33% in patients admitted to the ICU.\(^1\)\(^-\)\(^2\) Approximately 18% of these patients will develop alcohol withdrawal syndrome (AWS),\(^1\) whose symptoms can include physical and psychological manifestations that range from mild to life threatening. The four clinical stages of AWS are: autonomic hyperactivity, hallucinations, neuronal excitation, and delirium tremens (DTs).\(^3\) Milder symptoms can include hypertension, tachycardia, tachyplea, psychomotor agitation, nausea, vomiting, anxiety and hallucinations.\(^1\)\(^,\)\(^4\) Based on case series, 20% to 33% of patients with AWS will require ICU admission,\(^5\) and 5-20% of patients with AWS will progress to alcohol withdrawal delirium (AWD), also known as DTs, which can be a medical emergency.\(^3\)\(^-\)\(^4\) Symptoms of AWD may manifest between 24 and 96 hours after abstaining from alcohol and include seizures, hallucinations and a hyperadrenergic state.\(^1\)\(^-\)\(^2\)\(^,\)\(^4\) Mortality rates are upwards of 25% in patients with multiple medical comorbidities.\(^2\) Patients with AWS tend to have increased length of hospitalization, duration of intubation, infection, cost, and mortality.\(^2\)

Alcohol abuse causes an imbalance in inhibitory gamma-aminobutyric acid (GABA) neurotransmission and excitatory N-methyl-D-aspartate (NMDA) receptor stimulation.\(^2\) Chronic alcohol activation of the GABA receptor results in decreased endogenous GABA release and downregulation of receptors.\(^2\) Alcohol also inhibits the activity of NMDA receptors.\(^5\) Over time, this inhibition results in upregulation of receptor sensitivity in a compensatory attempt to maintain homeostasis.\(^6\) Additionally, alcohol has an inhibitory effect on the adrenergic system, which results in systemic upregulation and decreased regulation of neuronal firing.\(^2\)\(^,\)\(^5\) Abrupt cessation of alcohol intake results in a drastic decrease in inhibitory signaling for which the body's endogenous GABA signaling cannot compensate. Rebound glutamate signaling at the NMDA receptor and increased central nervous system excitatory tone, leading to a state of hyperexcitability presenting as the autonomic hyperactivity to DTs continuum previously mentioned.\(^2\)\(^-\)\(^3\)

Benzodiazepines, including lorazepam, diazepam, and midazolam, are the most commonly used and recommended agents for AWS.\(^5\)\(^,\)\(^7\) Benzodiazepines have been studied in numerous trials for the prevention and treatment of AWS symptoms and have shown to be effective.\(^5\) However, increasing doses of benzodiazepines place patients at risk for respiratory depression, aspiration, and intubation.\(^1\) Based on case series, 13% to 90% of ICU patients with AWS require intubation.\(^2\) Patients receiving continuous infusion benzodiazepines have an increased incidence of intubation compared with those who receive intermittent bolus dosing.\(^2\)\(^-\)\(^3\) In patients with AWD, benzodiazepine monotherapy may not be effective enough to control symptoms and may worsen delirium.\(^1\)\(^,\)\(^5\)

**Alpha-2 Agonists**
Both clonidine and dexmedetomidine are presynaptic \(\alpha_2\)-receptor agonists and exert their effect through a negative feedback mechanism. Stimulation of presynaptic \(\alpha_2\) receptors inhibits the release of norepinephrine and results in sympatholysis.\(^2\) Given the excitatory effect that alcohol withdrawal has on the adrenergic system, \(\alpha_2\) receptor agonists may have a role in therapy. Clonidine was approved by the Food and Drug Administration in 1974 for the treatment of hypertension.\(^4\) Prospective controlled trials have shown that clonidine is effective for treating AWS-related autonomic instability, including hypertension and tachycardia.\(^2\) Limitations of clonidine therapy include its long duration of action (the oral half-life is 12-16 hours) and limited forms (only available in oral and transdermal formulations) in the United States.\(^8\)
Dexmedetomidine is a lipophilic, intravenous-only derivative of clonidine, but it is eight times more selective for the α₂ receptor.²⁻³ It was approved by the Food and Drug Administration in 1999 for sedation in mechanically ventilated patients in the ICU and for procedural sedation in nonintubated patients for a maximum of 24 hours.¹⁴ Dexmedetomidine produces a state of “cooperative sedation” and has anesthetic, anxiolytic, analgesic and sympatholytic properties.⁸ Common adverse events associated with its use include bradycardia and hypotension. Notably, however, it does not cause respiratory depression. Due to its short half-life (2 hours), dexmedetomidine is administered as a continuous infusion, which allows for quick titration. A loading dose is optional but has been associated with hemodynamic instability.²

Evidence for Dexmedetomidine Use in AWS
No controlled trials are evaluating dexmedetomidine use for acute alcohol withdrawal in the critical care setting. However, several case series have been published.

Rayner et al¹ published a retrospective review of 20 consecutive patients admitted to an ICU and administered dexmedetomidine solely for AWS. Patients with cerebrovascular accidents or a history of severe head trauma were excluded. In addition to dexmedetomidine, patients also received lorazepam as needed. Data were collected for up to 24 hours prior to the start of dexmedetomidine and then for the first 24 hours of dexmedetomidine therapy. All patients survived their hospitalization and only one patient had to be intubated, although that patient received large doses of lorazepam. Five patients initially received a bolus dose of dexmedetomidine and none experienced any adverse events associated with the bolus. The mean dose of dexmedetomidine was 0.53 mcg/kg/h, and the mean length of therapy was 49.1 hours. The mean daily lorazepam dose fell 62% (52.7 mg to 20.3 mg) from the 24 hours prior to dexmedetomidine therapy to the first 24 hours after (P<0.001). One patient had a suspected adverse drug event associated with dexmedetomidine, two 9-second periods of asystole on telemetry that required discontinuation. A nonsignificant increase in bradycardia was observed after dexmedetomidine was initiated.

Dailey et al⁹ published an abstract of a retrospective chart review of 10 patients with AWS who were treated with dexmedetomidine. The mean dose was 0.7 mcg/kg/h (range: 0.1-1.5 mcg/kg/h) and the mean infusion time was 50 hours. After initiation of dexmedetomidine, patients’ mean Clinical Institute Withdrawal Assessment for Alcohol score decreased from 26± 5 to 13±9 (P=0.014). The mean diazepam usage 24 hours prior to dexmedetomidine initiation was 13 mg/h, falling to 3 mg/h in the 24 hours after treatment (P=0.013). No patient required intubation, although one developed pneumonia. Hypotension (systolic blood pressure <100 mm Hg) occurred in five patients, and dexmedetomidine was temporarily held in two patients due to episodes of significant hypotension (systolic blood pressure <75 mm Hg).

Muzyk et al¹⁰ published a retrospective review of five patients admitted to the ICU for AWS and given dexmedetomidine. None of the patients received a loading dose. The mean infusion dose was 0.22 mcg/kg/h (range: 0.04-0.7 mcg/kg/h) and the mean infusion time was 3 ± 1 days. Prior to receiving dexmedetomidine, patients received lorazepam at an average dose of 38.4 ± 32.4 mg/day. This increased to 80.2±49.2 mg/day following dexmedetomidine initiation; however, lorazepam usage fell to 23.6 ±12.9 mg/day at dexmedetomidine discontinuation. None of the patients required intubation and no patient had an episode of bradycardia or hypotension necessitating dexmedetomidine withdrawal.

DeMuro et al⁸ published a retrospective chart review of 10 patients who received dexmedetomidine for AWS. Hemodynamic data were collected for 4 hours prior to the initiation
of dexmedetomidine. In addition to dexmedetomidine, patients could receive as-needed boluses of benzodiazepines and haloperidol. None of the patients received a loading dose of dexmedetomidine. The mean infusion dose was 0.63 mcg/kg/h (range: 0.2–1.2 mcg/kg/h) and the mean infusion time was 92.7 hours. Dexmedetomidine was the sole agent used in three patients. Three patients required intubation. A nonsignificant decrease in heart rate and blood pressure occurred during the first 4 hours of dexmedetomidine therapy compared to the 4 hours prior, but no patient had the agent discontinued due to hemodynamic instability. Three patients had treatment failure with dexmedetomidine, meaning that the therapy was discontinued due to failure to control agitation. There were no deaths, no incidences of aspiration pneumonia, and no seizures reported.

The only prospective study was published by Tolonen et al. This was an, observational study that evaluated 18 consecutive patients admitted for AWS. The primary outcome was the resolution of delirium defined by Confusion Assessment Method for the ICU and Richmond Agitation and Sedation Scale. Benzodiazepines and haloperidol could be given as needed to attain a score of zero on the latter test. Per hospital policy, if benzodiazepines and haloperidol failed to control agitation, or if the patients were deemed unlikely to tolerate increased benzodiazepine doses, they could be given dexmedetomidine, which was initiated on day 1-3 after admission. The maximum dose of dexmedetomidine was 1.5 mcg/kg/min, and the mean length of administration was 23.9 hours. The mean time to resolution of delirium symptoms was 3.8 days. No patients required intubation, but one patient died of acute pancreatitis. No adverse events associated with dexmedetomidine were observed.

An ongoing prospective, double-blind randomized control study is evaluating the efficacy of dexmedetomidine for AWS and alcohol withdrawal delirium in adult critically ill patients. The primary outcome is ICU length of stay. The anticipated enrollment is 150 patients, and the trial is expected to be completed in 2015.

Discussion

Acute alcohol withdrawal remains a widespread problem in hospitalized patients. Although benzodiazepines remain the mainstay in treatment for alcohol withdrawal syndrome, adjunctive α2 receptor agonists may have a role in therapy to help control hyperadrenergic output in patients who are not controlled with benzodiazepines alone or are at increased risk of experiencing respiratory depression from benzodiazepine therapy. Dexmedetomidine is only available as a brand-name product, although its patent is expected to end at the end of 2013. It is still a resource-intensive medication, whose role in therapy is not yet fully elucidated. Retrospective case series have demonstrated its safety, although prospective, controlled trials are still needed to prove efficacy in patients who are experiencing AWS in the acute care setting.

References