

Beyond Benzodiazepines For Severe Ethanol Withdrawal

Benzodiazepines remain the backbone of effective ethanol withdrawal management. One of the most common mistakes we make in managing severe ethanol withdrawal is not giving enough benzodiazepines for fear of respiratory depression. Once a large quantity of benzodiazepines has been administered, there are additional and adjunctive pharmacologic options to consider. This session will discuss these options and provide evidence for or against their use.

Dexmedetomidine

BACKGROUND

Alpha-2 agonists that reduce sympathetic output may be effective adjunct treatment modalities without suppressing respiratory drive. Some older studies using clonidine demonstrated possible benefit. Similarly, there are several case reports and four case series using dexmedetomidine (a parenteral alpha-2 agonist) in addition to benzodiazepines. In 2014, the first randomized, placebo controlled trial was published evaluating dexmedetomidine in this role. FDA-approved dosing is 0.2-0.7 mcg/kg/hr as a continuous infusion. (Muzyk AJ, et al. *Ann Pharmacother* 2011;45(5):649-57. PMID 21521867.)

THE DATA

2012 – Case Series

1. A retrospective case series of 10 ICU patients demonstrated safety of dexmedetomidine for ethanol withdrawal. Only 3 patients needed intubation, less benzodiazepines were required, heart rate was reduced up to 10 bpm, and blood pressure was decreased up to 3 mm Hg. Maximum dexmedetomidine dose used was 1.2 mcg/kg/hr. (DeMuro JP, et al. *J Anesth* 2012;26(4):601-5. PMID 22584816.)
2. A retrospective case series of 20 ICU patients demonstrated a 62% reduction in benzodiazepine dosing after initiation of dexmedetomidine and a 21% reduction in alcohol withdrawal severity score. Only one patient required intubation. Dexmedetomidine was stopped in one patient who had two 9-second asystolic pauses noted on telemetry. (Rayner SG, et al. *Ann Intensive Care* 2012;2(1):12. PMID 22620986.)

2013 – Case Series

1. A prospective case series of 18 ICU patients further demonstrated safety of dexmedetomidine for ethanol withdrawal when administered for a mean 24 hours. No patients required intubation. Time to resolution of alcohol withdrawal was 3.8 days, with and ICU length of stay 7.1 days, and hospital length of stay 12.1 days. Maximum dexmedetomidine dose used was 1.5 mcg/kg/hr. (Tolonen J, et al. *Eur J Emerg Med* 2013;20(6):425-7. PMID 23247391.)

2. A retrospective case series of 33 ICU patients used dexmedetomidine as an adjunct therapy to benzodiazepines titrating to a rate of 0.7 mcg/kg/hr. In the 12 hours after dexmedetomidine began, patients experienced a 20 mg reduction in median cumulative benzodiazepine dose used ($P < 0.001$), a 14 mmHg lower mean arterial pressure ($P = 0.03$), and a 17 bpm reduction in median heart rate ($P < 0.001$). Four (12%) patients experienced hypotension (systolic blood pressure < 80 mmHg) during therapy and there were no cases of bradycardia (heart rate < 40 bpm). (Frazee EN, et al. *J Crit Care* 2014;29(2):298-302. PMID 24360597.)

2014 – The First Randomized Trial

1. A new randomized, double-blind trial evaluated 24 ICU patients with severe ethanol withdrawal. Group 1 received: Lorazepam + Placebo, Group 2 received: Lorazepam + Dexmedetomidine (doses of 0.4 mcg/kg/hr and 1.2 mcg/kg/hr). Pertinent results include the following: 24-hour lorazepam requirements were reduced from 56 mg to 8 mg in the dexmedetomidine group ($p=0.037$); 7-day cumulative lorazepam requirements were similar; Clinical Institute Withdrawal Assessment or Riker sedation-agitation scale scores were similar between within 24 hours; and bradycardia occurred more frequently in the dexmedetomidine group. (Mueller SW, et al. *Crit Care Med* 2014;42(5):1131-9. PMID 24351375.)

APPLICATION TO CLINICAL PRACTICE

In my opinion, a major limitation of this study is that patients had more than 24 hours of treatment before randomization. Eleven of the 24 patients were already intubated when the trial started. The best place to use dexmedetomidine is in the early treatment course to help avoid intubation altogether. I'm not sure this very exclusive trial (24 patients included/209 excluded over 4 years) provides any answers for the patients who may benefit most from this therapy. I really feel a reduction in benzodiazepines is not even the correct outcome to measure. That may lead to the erroneous notion that we don't need benzodiazepines. We should be looking at reduction in intubations and ICU length of stay.

Crispo et al. studied 61 nonintubated patients that received either dexmedetomidine or benzodiazepine infusions in addition to standard alcohol withdrawal management. The primary outcome was a composite endpoint including rates of respiratory distress requiring endotracheal intubation or occurrence of alcohol withdrawal seizures. No significant differences in the composite end point were noted between the BZD and DEX groups or its individual components of respiratory distress or alcohol withdrawal seizures. The DEX group received a lower median total dose of lorazepam equivalents after initiation of the study drug, but this did not translate into a reduced requirement for endotracheal intubation or decreased length of stay. DEX

was associated with more adverse drug events including hypotension and bradycardia. Of concern, DEX may impair the ability to assess symptoms appropriately and administer BZDs in a symptom-triggered fashion. Although the total cost of hospitalization was similar between groups, DEX was associated with a higher study drug cost per patient. DEX demonstrated a BZD-sparing effect in the treatment of AWS; however, this surrogate end point should be interpreted with caution. Although this study cannot disprove the possibility of a protective effect of DEX in preventing the requirement for endotracheal intubation in patients with AWS, an increased rate of adverse drug events and increased study drug costs were observed. If DEX is used in clinical practice, it should only be used as adjunctive therapy with BZDs that have a proven benefit in AWS. (Crispo AL, et al. *Pharmacotherapy* 2014;34(9):910-7. PMID 24898418.)

KEY POINTS

With the results of an RCT with a comparison group, there are a few take home points worth mentioning:

- Dexmedetomidine may be a useful adjunct to benzodiazepines for ethanol withdrawal patients (in the ED or ICU).
- Reduced benzodiazepine requirements have been observed, but the RCT demonstrated this only in the short-term (24 hours). However, the RCT intervention didn't start until 24 hours of treatment were already given. A major limitation is that 11 of 24 patients were intubated prior to the start of dexmedetomidine.
- Dexmedetomidine does not suppress the respiratory drive and can be administered to non-intubated patients.
- Bradycardia and possibly hypotension are the major adverse effects with dexmedetomidine use.
- Benzodiazepines are still first line therapy for ethanol withdrawal, but dexmedetomidine may be a useful adjunct and can be used in non-intubated patients.

Ketamine

BACKGROUND

In addition to the down regulation of GABA receptors in chronic ethanol users, there is an upregulation in NMDA receptor subtypes. Although the pathophysiology is much more complex, when ethanol abstinence occurs, there is a shortage of GABA-mediated CNS inhibition and a surplus of glutamate-mediated CNS excitation. If GABA agonists are the mainstay of treatment, why not also target the NMDA receptor? Enter ketamine.

THE DATA

Only one study exists and was published recently (Wong A, et al. *Ann Pharmacother* 2015;49(1):14-9. PMID 25325907). The study was a retrospective review of 23 adult patients from April 2011 to March 2014 who were administered ketamine specifically for management of AWS. Ketamine was initiated primarily with

toxicology consultation for significant BZD requirements or delirium tremens. The mean time to initiation of ketamine from first treatment of AWS, and total duration of therapy were 33.6 and 55.8 hours, respectively. Mean initial infusion dose and median total infusion rate during therapy were 0.21 and 0.20 mg/kg/h, respectively. There was no change in sedation or alcohol withdrawal scores in patients within 6 hours of ketamine initiation. The median change in BZD requirements at 12 and 24 hours post-ketamine initiation were -40.0 and -13.3 mg, respectively. The mean time to AWS resolution was 5.6 days. There was one documented adverse reaction of oversedation, requiring dose reduction. The authors concluded that ketamine appears to reduce BZD requirements and is well tolerated at low doses.

APPLICATION TO CLINICAL PRACTICE

While the dexmedetomidine studies should not be using reduction in benzodiazepine requirements as an endpoint, it may be acceptable for ketamine since it actually works on the underlying pathophysiology. More studies are needed but I'm glad to see we're starting to look at it.

Barbiturates and Propofol

BACKGROUND

"In instances of extreme benzodiazepine resistance, patients often receive a second GABAergic drug because of "failure" of benzodiazepine therapy." (Goldfrank's Toxicologic Emergencies)

THE DATA

Phenobarbital can be given in combination with benzodiazepines (or by itself) in doses of 130 mg or 260 mg IV. The onset of effect is a bit delayed compared to benzodiazepines (20-40 minutes), so it is important not to give too many doses close together to avoid 'stacking' of clinical effects and an increased risk of respiratory depression. (Hill A, et al. *J Subst Abuse Treat* 1993;10:449-51. PMID 8246319.) (Ives TJ, et al. *South Med J*. 1991;84:18-21. PMID 1986421.) (Rosenson J, et al. *J Emerg Med* 2013;44(3):592-8. PMID 22999778.) One study used escalating bolus doses of diazepam (up to 200 mg) combined with phenobarbital in subjects with continued benzodiazepine resistance (defined as the requirement for bolus doses more frequently than every hour). The authors found a reduced need for mechanical ventilation by nearly 50%.

Propofol is an additional alternative, given its purported effect on the GABA system. Standard doses can be used. Remember that prolonged infusions of propofol is associated with propofol infusion syndrome and other metabolic disturbances. Propofol was safely administered to 21 patients in an observational study. The patients were intubated for severe benzodiazepine resistant DTs and given propofol. Propofol should generally only be used in the setting of mechanical ventilation. Propofol also antagonizes NMDA receptors and can reduce the excitatory piece of AWS. (McCowan C, et al. *Crit Care Med* 2000;28:1781-4. PMID 10890619) (Lorentzen K, et al. *Dan Med J* 2014;61(5):A4807. PMID 24814732.)

Magnesium

We love magnesium for everything. Why not alcohol withdrawal? Alcoholics usually have deficiency of magnesium, right? It also is pretty good at preventing seizures in other disorders such as eclampsia. In addition, magnesium deficiency has many clinical similarities to AWS which can make the diagnosis challenging. Several studies have evaluated the efficacy of magnesium supplementation. But, in a randomized, placebo-controlled trial, intravenous magnesium sulfate had no effect on either severity of alcohol withdrawal or incidence of withdrawal seizures. So unfortunately, aside from repletion of electrolyte abnormalities, there is no indication for routine administration of magnesium for the treatment of AWS.

(Wilson A, et al. *Alcohol Clin Exp Res*. 1984;8:542-5. PMID 6393805)

Baclofen

Baclofen mainly works on GABA-B receptors (benzodiazepines work on GABA-A), so there is some thought that baclofen could be a potential adjunctive agent for AWS. There have been a few randomized trials with baclofen, but so far there is insufficient evidence to support its use in this clinical scenario. (*Cochrane Database Syst Rev* 2013;2:CD008502. PMID 23450582).

Gabapentin

Gabapentin is structurally related to GABA (heck, that's where it got its name)! However, it does not bind to GABA-A or GABA-B receptors, and it does not appear to influence synthesis or uptake of GABA. One trial in 37 patients with severe alcohol withdrawal symptoms evaluated gabapentin. Patients were given gabapentin 800 mg, and if their symptom score reduced within 2 h, they were termed 'early responders' and were then treated for 2 days with 600 mg gabapentin q.i.d. (i.e. a total of 3200 mg in the first 24 h) before beginning a taper. Twenty-seven (73%) were early responders (baseline CIWA-AR improved from 17.3 +/- 2.6 to 8.0 +/- 3.6 points). In the remaining 10 patients, baseline CIWA-AR deteriorated within 2 h (from 20.1 +/- 4.6 to 21.5 +/- 4.65 points). These patients were switched to clomethiazole (n = 4) or clonazepam (n = 6), which is the usual treatment. The authors concluded that oral 800 mg gabapentin (loaded up to 3200 mg in the first 24 h) is helpful only in reducing less severe and less complicated acute AWS. Therefore, you probably won't see it being used in the refractory cases. (Bonnet U, et al. *Alcohol Alcohol* 2010;45(2):143-5. PMID 20019070.)