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Session Title: Beyond Benzodiazepines for Severe Ethanol Withdrawal

Session overview

Benzodiazepines remain the backbone of effective ethanol withdrawal management, yet one of the most common mistakes we make is not giving enough 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.

Objectives

- In a patient who has received significant doses of benzodiazepines for ethanol withdrawal and is either too sedated or not controlled, determine when alternative or adjunctive agents should be administered.
- Evaluate the role of phenobarbital, propofol, and dexmedetomidine in ED patients with severe ethanol withdrawal.

Barbiturates

ADVANTAGES OVER BENZODIAZEPINES (Hill, J Subst Abuse Treat 1993)

1. Doesn't cause delirium like benzos can (Moore, J Med Toxicol 2014)
2. Doesn't cause paradoxical reactions (Ives, South Med J 1991)
3. Linear correlation between phenobarbital dose and blood concentration (Tangmose, Dan Med Bull 2010)
4. Compares favorably to benzos in RCT of severe withdrawal (Kramp, Acta Psychiatr Scan 1978)
5. Evidence to avoid ICU admissions (Rosenson, J Emerg Med 2013)
6. Evidence to avoid mechanical ventilation (Gold, Crit Care Med 2007)

EVIDENCE

1. An RCT comparing phenobarbital (260 mg IV followed by 130 mg IV PRN) vs. lorazepam for 44 patients presenting to the ED with mild to moderate alcohol withdrawal. Most were discharged home. The two treatments were equivalent, although the study was underpowered. (Hendey, Am J Emerg Med 2011)
2. 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%. (Gold, Crit Care Med 2007)
3. A prospective, randomized, double-blind, placebo-controlled study where 102 patients were randomized to receive either a single dose of IV phenobarbital (10 mg/kg in 100 mL normal saline) or placebo (100 mL normal saline). All patients were placed on the institutional symptom-guided lorazepam-based alcohol withdrawal protocol. Patients that received phenobarbital had fewer ICU admissions (8% vs. 25%, 95% confidence interval 4-32). There were no differences in adverse events. (Rosenson, J Emerg Med 2013)

CLINICAL PEARLS

- Phenobarbital can be given in combination with benzodiazepines (or by itself)
- Doses of 130 mg or 260 mg IV, although up to 10 mg/kg has been studied (administered over 30 minutes)
- 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

Propofol

Propofol is an additional alternative, given its purported effect on the GABA system. Propofol also antagonizes NMDA receptors and can reduce the excitatory piece of AWS. Standard doses can be used. Propofol was safely administered to 4 patients in an observational study (McCowan, Crit Care Med 2000). Separately, 15 patients were intubated for severe benzodiazepine resistant DTs and given propofol (Lorentzen, Dan Med J 2014). Compared to benzodiazepine infusion monotherapy, propofol use had similar outcomes (Sohraby, Ann Pharmacother 2014). Propofol should generally only be used in the setting of mechanical ventilation.

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. (Muzyk, Ann Pharmacother 2011)

CASE SERIES

1. Retrospective case series of 10 ICU patients reported that 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. Max dose was 1.2 mcg/kg/hr. (DeMuro, J Anesth 2012)
2. 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, Ann Intensive Care 2012)
3. Prospective case series of 18 ICU patients reported no patients required intubation and time to withdrawal resolution 3.8 days. Max dose was 1.5 mcg/kg/hr. (Tolonen, Eur J Emerg Med 2013)
4. Retrospective case series of 33 ICU patients titrated 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 patients experienced hypotension (systolic blood pressure < 80 mmHg). (Frazee, J Crit Care 2014)

TRIALS

1. A 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). 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, Crit Care Med 2014)
    a. My thoughts: 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.
2. Another controlled trial randomized 72 ICU patients to receive dexmedetomidine 0.2-1.4 µg/kg/h with symptom-triggered BZD (10 mg diazepam bolus) or only symptom-triggered 10 mg boluses of diazepam. Median 24-h diazepam consumption was lower in the intervention group (20 vs. 40 mg, $p < 0.001$), as well as median cumulative diazepam dose during the ICU stay (60 vs. 90 mg, $p < 0.001$). Bradycardia was common in the dexmedetomidine group (10 vs. 2; $p = 0.03$). (Bielka, Ann Intensive Care 2015)
    a. My thoughts: Even if benzodiazepine reduction was a good outcome to measure (I don't think that it is), a 20 mg decrease in diazepam between the groups is not a clinically meaningful change that warrants a high-cost medication such as dexmedetomidine. If patients only received 60-90 mg of diazepam during their ICU stay, then these clearly weren't severe withdrawal patients.
3. Retrospective cohort study of 20 patients receiving dexmedetomidine matched to 22 control patients. Mean 12-hour change in benzodiazepine requirement was lower for dexmedetomidine versus control (-20 vs -8.3 mg, $P = 0.0455$) but not at 24 hours (-29.6 vs -11 mg, $P = 0.06$). Patients receiving dexmedetomidine experienced more bradycardia than controls (35% vs 0%, $P < 0.01$) but not hypotension. (VanderWeide, J Intensive Care Med 2016)
    a. My thoughts: Interestingly, the study periods of the two studies by the same authors overlap and it appears many of the same patients were in both studies. In fact, Dr Lewis Nelson (@LNelsonMD) and I published a letter to the editor in response to this study, citing several problems. Although the study is titled "Early Dexmedetomidine Addition..." patients were enrolled up to 60 hours after hospital admission. (Hayes BD, J Intensive Care Med 2016)

KEY POINTS

- Dexmedetomidine may be a useful adjunct to benzodiazepines for ethanol withdrawal patients (in the ED or ICU).
- Reduced benzodiazepine requirements have been observed in both RCTs, but only in the short-term (24 hours).
- Dexmedetomidine does not suppress the respiratory drive and can be administered to non-intubated patients. Bradycardia and hypotension are the major adverse effects.

- Benzodiazepines are still first, second, and third line therapy for ethanol withdrawal. Other GABA agents such as phenobarbital and propofol remain good next line options after benzodiazepines. Even ketamine may have a future role, with the first study published in 2015.
- Future studies should stop looking at a reduction of benzodiazepine requirements as an endpoint and instead focus on outcomes such as reduction in intubations and ICU admissions. They should also evaluate dexmedetomidine earlier in the severe withdrawal course, but only after appropriately high benzodiazepines (or barbiturates) have been administered.

Ketamine

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.

Only one study exists (Wong, Ann Pharmacother 2015), a retrospective review of 23 adult ICU patients. Ketamine was initiated primarily with toxicology consultation for significant BZD requirements or DTs. 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. 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.

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.

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, Alcohol Clin Exp Res 1984)

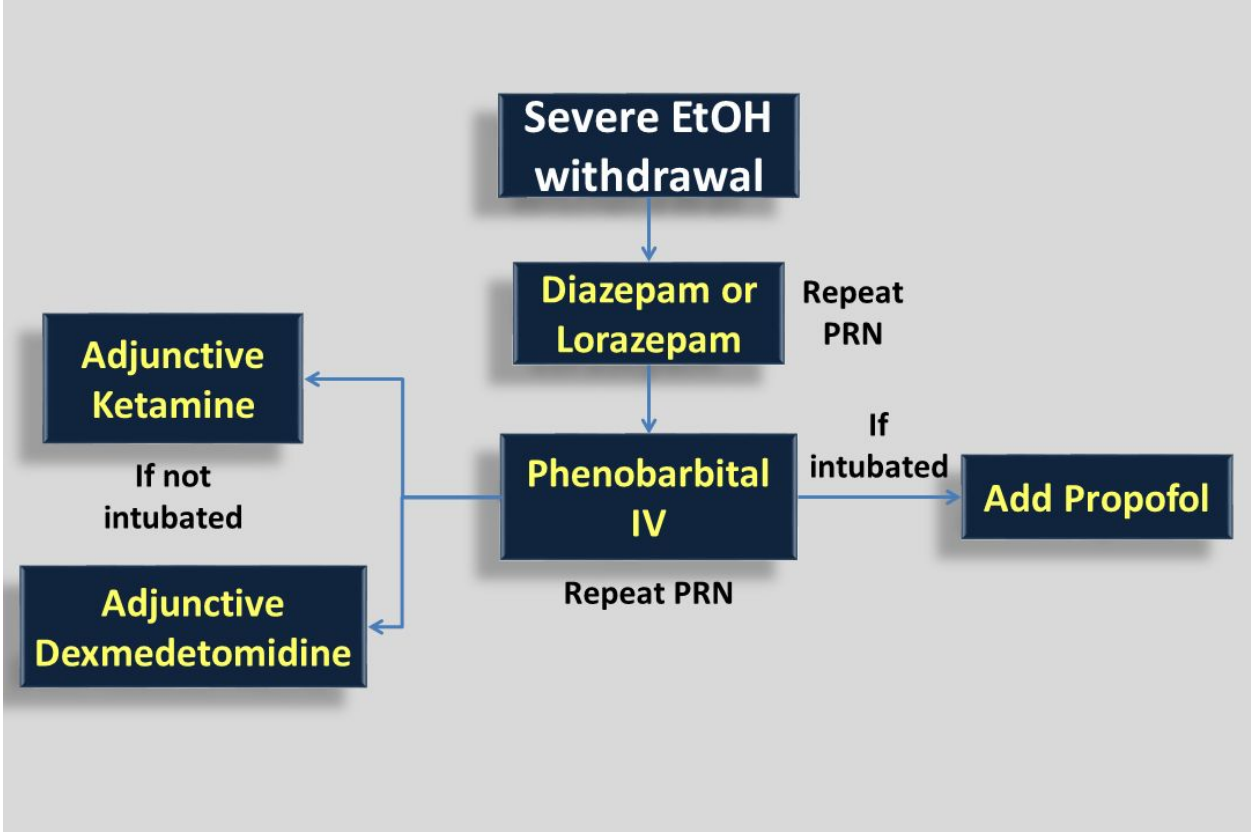
Baclofen

Baclofen mainly works on GABA-B receptors (benzos work on GABA-A), so perhaps baclofen could be a potential adjunctive agent for AWS. There have been a few RCTs with baclofen, but so far there is insufficient evidence to support its use in this clinical scenario. (Cochrane Database Syst Rev 2013)

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 found that gabapentin 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, Alcohol Alcohol 2010)

My Algorithm



Further reading

Academic Life in EM: Dexmedetomidine as an Adjunct to Benzodiazepines for Ethanol Withdrawal

Dr. Josh Farkas (@Pulmcrit) outlines the advantages of phenobarbital in 3 EMCrit blog posts:

1) Treating delirium tremens: Pharmacokinetic engineering with diazepam and phenobarbital (December 30, 2014)
2) Phenobarbital monotherapy for alcohol withdrawal: Simplicity and power (October 18, 2015)
3) Phenobarbital monotherapy for alcohol withdrawal: Reloaded (December 13, 2017)

REBEL EM summarizes the available data: Benzodiazepine-Refractory Alcohol Withdrawal