Benzodiazepine Resistant Alcohol Withdrawal Seizures: Where are we now?
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Definition/background

- Extensive alcohol use promotes a number of physiologic changes in consumers. When alcohol is withheld, a number of life-threatening conditions can precipitate. Delirium tremens (DTs), also known as alcohol withdrawal delirium in the DSM-IV, is a significant complication of alcohol withdrawal. It requires aggressive management to facilitate positive patient outcomes.
- DTs are characterized by **hallucinations, diaphoresis, hyperthermia, tremors, and other signs of sympathetic hyperactivity**. Assessment of alcohol withdrawal/DTs can be done in a number of ways, one of which is the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A). The CIWA and its revisions (CIWA-Ar) represent one objective and systematic way to assess patients' symptoms based on a number of physiologic measurements such as tremulousness, hallucinations, and diaphoresis. These symptoms, in conjunction with changes in vital signs (hypertension, tachycardia, hyperthermia) reflect the constellation of symptoms that commonly make up alcohol withdrawal syndrome/DTs.

Pathophysiology

- Ethanol acts as a depressant on the central nervous system (CNS) via its activity on a number of receptors. It is believed to **increase the activity of the GABA inhibitory transmitter and decrease the excitatory activity of glutamate via the NMDA receptor**. [1] Chronic alcohol use can induce physiologic changes to the CNS in a phenomenon known as **tolerance**. If alcohol consumption ceases in an individual whose body has adapted to its continual presence, the lack of the depressant activity of alcohol results in a hyperactive state that clinically presents as the symptoms seen in acute withdrawal syndrome.
- Repeat episodes of alcohol cessation after extensive use results in a worsening of subsequent excitability states in a phenomenon described as **kindling**. [2] In mice, authors showed how the worsened hyperexcitability states were prevented by administration of benzodiazepines during the earlier, milder hyperexcitability episodes. Thus, the early treatment of withdrawal episodes is integral in the prevention of worse and potentially more detrimental events.

What is resistant AWS/DT?

- Considering the consequences of unchecked alcohol withdrawal syndrome and its development to DTs, it is important to treat the syndrome effectively and early in its clinical course. The gold standard for treatment is **benzodiazepines**, which act on the GABA receptor complex, basically substituting for ethanol. Appropriate dosing of benzodiazepines in AWS can be determined by a number of clinical indicators, including normalization of vital signs, sedation with easy arousability, and cessation of hallucinations. However, there have been cases of alcohol withdrawal syndrome that are resistant to treatment with benzodiazepines in regular doses, requiring large doses and occasionally a second sedative agent to maintain physiologic stability. These cases of withdrawal syndromes resistant to the standard of care are identified as resistant alcohol

withdrawal (RAW). Hack (2006) describes RAW as alcohol withdrawal requiring an additional sedative (of a different drug class) within the first 24 hours of symptom onset or if vital sign abnormalities not otherwise explained continued at 24 hours of benzodiazepine treatment. [3] Gold *et al* (2007) review a number of studies and note one that utilized the defined benzodiazepine-resistant alcohol withdrawal syndrome as the need for >40mg diazepam in one hour. [4] Regardless of the variations in the definition of resistant AWS, the need to sufficiently treat the symptoms of AWS may prompt clinicians to look outside of the normal standard of care to suitably and appropriately treat their patients. Considering this, secondary sedative agents may be considered as adjuncts to benzodiazepines.

Treatment considerations in benzodiazepine resistant AWS:

- **Elevated doses of benzodiazepines** - Gold *et al* (2007) describes a protocol that utilized escalating bolus doses of benzodiazepines (to a maximum of 100-150mg), then augmented treatment with doses of phenobarbital after determining during a prior observation period that patients were "undertreated." The researchers were able to show **decreased need for intubation (commonly as a result of the addition of a continuous secondary sedative agent) but no improvement in ICU length of stay or the incidence of hospital-acquired pneumonia**. [4]
- **Phenobarbital** - Gold *et al* (2007) also note the use of relatively low doses of Phenobarbital (65/130/260mg) as an adjunct to benzodiazepine treatment. They describe a **two-fold reduction in the need for intubation** and continuous sedation when benzodiazepines and phenobarbital were used together. Both medications have the same target of action (GABA) and the authors note that barbiturates may augment the activity of benzodiazepines while also diminishing the effects of the stimulatory neurotransmitter glutamate. [4]
- **Propofol** - A number of case descriptions are available regarding the use of propofol in AWS, but Lorentzen *et al* (2014) describe a retrospective study examining the use of propofol infusions for 48 hours to treat delirium tremens uncontrolled by benzodiazepines, chlordiazepoxide, or phenobarbital. They note successful treatment of 12 out of 15 patients evaluated, but 13 of the 15 patients had a long period of continued sedation after the infusion was stopped. The study did not compare use of propofol and benzodiazepines to benzodiazepines alone, and noted further study with propofol is required. [5] Gold *et al* (2007) note the effects of propofol to include **activation of GABA and inhibition of NMDA**, both crucial in the management of AWS. [4]
- **Baclofen** - A Cochrane Database Systematic review published in 2011 and updated in 2013 discussed two randomized controlled trials involving baclofen, another GABA agonist, in alcohol withdrawal. One study examined the ability and safety of baclofen for acute uncomplicated alcohol withdrawal syndrome, compared to diazepam. Researchers found both groups had a decrease in CIWA-Ar subgroup scores without any difference between the baclofen and diazepam treated groups. Additionally, they found no safety issues in the baclofen treated group. The second study analyzed CIWA-Ar scores in baclofen versus placebo and benzodiazepine dose amounts in baclofen versus placebo groups, and found no difference in scores between the baclofen and placebo group. Additionally, the second paper found a decreased need for high-dose benzodiazepines in the baclofen group when compared to the placebo group. Despite the findings of the

second paper, the authors of the Cochrane review found the **evidence insufficient to recommend baclofen for treatment of AWS**. [6]

- **Dexmedetomidine** - Dexmedetomidine is a central alpha-2 agonist that has recently been examined for its ability to provide **sedation without respiratory depression**. Mueller *et al* (2014) devised a dose range study of high- and low-dose dexmedetomidine versus placebo in patients who had elevated CIWA scores after receiving ≥16mg lorazepam/4 hours, examining the ability of dexmedetomidine to serve as an adjunct to regular benzodiazepine treatment for withdrawal. The authors found a **decrease in 24 hour lorazepam usage, but no statistically significant decrease in 7 day total lorazepam requirements**. [7]
- **Carbamazepine** - Carbamazepine is utilized as an anticonvulsant and mood stabilizer, but authors have examined its efficacy in treating AWS. Minozzi *et al* (2010) reviewed current literature relating to the use of anticonvulsants but **did not find enough evidence to merit their use as a regular treatment for AWS**. [8] The review did not comment on the use of carbamazepine as an adjunct to treatment or if it can serve a beneficial role in treating AWS resistant to benzodiazepines.

Complications

- Adjunct treatments, though beneficial when utilized to control AWS resistant to benzodiazepines, are not without side effects. One of the metrics in Gold *et al*'s (2007) paper was to observe the **ICU length of stay and the incidence of nosocomial infections** in intubated and non-intubated patients. [4] One of the major concerns of increased sedation is the need for endotracheal intubation and the associated risk increases in hospital-acquired infections and complications relating to the procedure.
- The use of escalating doses of dexmedetomidine can result in **bradycardia** necessitating de-escalation or additional supportive care. [7] Clinicians must understand the implications of adjunctive treatments and weigh their benefits with the risk of unintended side effects.

Conclusion

- The short- and long-term complications of alcohol withdrawal syndrome range from **physiological instability to intractable seizures and death**. The treatment focuses on **stabilization of vital signs and prevention of more severe withdrawal symptoms**. Intractable or resistant symptoms require more aggressive treatment regimens that incorporate high levels of benzodiazepines, potentially in addition to other sedatives, including propofol, phenobarbital, or baclofen. Continued study in the field of benzodiazepine-resistant alcohol withdrawal syndrome is necessary if clinicians are to provide the best care possible for their patients suffering from DTs.

Resources

[1] Tintinalli's Emergency Medicine. Chapter 179: Alcohols. Jennifer C Smith, Dan Quan
[2] Ulrichsen, Bech, Allerup, Hemmingson. Diazepam prevents progression of kindled alcohol withdrawal behavior. Psychopharmacology (1995) 121: 451-460.
[3] Hack, Hoffman, Nelson. Resistant alcohol withdrawal: Does an unexpectedly large sedative requirement identify these patients early? J of Med Tox (2006) 2: 5-10

[4] Gold, Rimal, Nolan, Nelson. A strategy of escalating doses of benzodiazepines and Phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med (2007) 35. 3: 724-730.
[5] Lorentzen, Oberg Lauritsen, Ole Bendtsen. Use of propofol infusion in alcohol withdrawal-induced refractory delirium tremens. Dan Med J (2014) 61: 1-5.
[6] Liu, Wang. Baclofen for alcohol withdrawal (Review). Cochrane Systemic Review (2013). 1-18.
[7] Mueller, Preslaski, Kiser, Fish, Lavelle, Malkoski, MacLaren. A randomized, double-blind, placebo-controlled dose range study of dexmedetomidine as adjunctive therapy for alcohol withdrawal. Crit Care Med (2014). 42(5) 1131-9.
[8] Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal (Review). Cochrane Systemic Review. (2010) 1-131.
[9] Eyer F, Schreckenberg M, Hecht D, Adorjan K, Schuster T, Felgenhauer N, Pfab R, Strubel T, Zilker T. Carbamazepine and valproate as adjuncts in the treatment of alcohol withdrawal syndrome: A retrospective cohort study. Alcohol and Alcoholism (2011). 46(2) 177-184.