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ALCOHOL WITHDRAWAL

SUMMARY

Alcohol withdrawal syndrome (AWS) is common in surgical and traumatically injured patients. Patients at risk must be identified and watched carefully for the development of symptoms. The mainstay of treatment is benzodiazepines. Controversy exists as to who should receive treatment, how to administer benzodiazepines, and which benzodiazepine to use. Adjunctive forms of treatment include beta-blockers, clonidine, and haldol. Other frequently practiced, yet less investigated treatments, include intravenous and oral ethanol.

RECOMMENDATIONS

- **Level 1**
 - **Benzodiazepines are the agents of choice in preventing alcohol withdrawal seizure activity**
 - **Long acting agents such as diazepam may provide a "smoother withdrawal."**
 - **Routine alcohol withdrawal prophylaxis is not necessary**
- **Level 2**
 - **Short acting agents such as oxazepam may have an increased incidence of seizure activity**
- **Level 3**
 - **Patients with a prior history of alcohol withdrawal seizures should receive prophylaxis**

INTRODUCTION

Alcohol is one of the most abused drugs worldwide. Alcohol abuse is a major public health problem with an estimated 5% of Americans being "heavy" alcohol consumers and nearly half a million in treatment for alcoholism at any one time. Alcohol abuse is a common medical comorbidity in the surgical, trauma, and critically ill patient population. Alcohol withdrawal syndrome (AWS) represents a well-known and frequently documented constellation of signs and symptoms. The development of AWS increases patient morbidity and complicates patient care. Effective control of these signs and symptoms is necessary to reduce harm to the patient, especially in the critical care setting where potentially lifesaving catheters and monitoring devices are frequently indwelling and at risk for self-removal by the agitated patient. Prompt recognition and treatment of AWS is essential.

AWS ranges from mild signs and symptoms to life-threatening seizure activity and delirium tremens. It is frequently encountered when patients fail to continue their normal ethanol ingestion due to hospitalization or injury. The complex pathophysiology of AWS is well described in a review article by Spies et al (5). Central nervous system excitation and autonomic hyperactivity are commonly encountered 24 to 48 hours following the cessation of ethanol intake. In most circumstances, these symptoms (tachycardia,

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

hyperreflexia, hypertension, nausea, vomiting, tremor, anxiety, agitation, insomnia, sweating) are mild and do not require pharmacologic intervention.

Symptom severity worsens with the magnitude and chronicity of alcohol abuse. The primary treatment goal in AWS is recognition and prevention of this potentially lethal clinical state. Withdrawal seizures may develop and are seen in 5-15% of patients presenting with signs of alcohol withdrawal. Approximately 5% will develop delirium tremens, a true medical emergency manifested by profound hyperactivity, clouding of consciousness, confusion, disorientation, diaphoresis and auditory and visual hallucinations with an estimated mortality of 5-15%. Death is usually the result of cardiac arrhythmias or respiratory failure. This is typically seen 3 to 5 days following cessation of alcohol intake.

Other causes for delirium and agitation must always be considered. First and foremost is unrecognized hypoxia. Other potential etiologies include drug interactions and other organic causes. Numerous medications have been implicated including those with anticholinergic properties (atropine, antihistamines), steroids, meperidine (and its metabolite normeperidine), cimetidine, several antimicrobials (penicillin, primaxin), and several common cardiovascular drugs (lidocaine, propranolol, digoxin). Cimetidine inhibits the liver's cytochrome P-450 enzyme system and has the potential to increase the toxicity of agents used to treat delirium including benzodiazepines. In the young or elderly and those patients with liver disease and/or low serum albumin concentration, benzodiazepines themselves can cause paradoxical central nervous system excitation. The potential for withdrawal from other illicit substances of abuse must also be considered.

Treatment begins with the recognition of patients at risk for AWS. These patients should be closely evaluated for signs and symptoms of AWS with the intent to prevent development of the more serious stages of the disease process. Various scales and questionnaires exist to evaluate patients for possible alcohol misuse (CAGE, SMAST) (2). It is vital to identify patients with a previous history of alcohol-related seizure activity or delirium, for these patients are at an elevated risk for recurrence and may warrant empiric therapy. Other risk factors include duration of the abuse process (> 6 years), markedly elevated blood alcohol levels, and associated medical illnesses such as alcoholic gastrointestinal disease and elevated liver enzymes which are markers of underlying alcohol abuse. Mechanical ventilation and sedation may mask the signs and symptoms of AWS and make use of the various alcohol abuse prediction scales and questionnaires problematical. Prompt recognition may therefore be difficult and treatment delayed in the critically ill. Friends and family may be reluctant to fully disclose the patient's true daily alcohol intake. Close monitoring and a high index of suspicion are essential.

The mainstay of AWS treatment is the liberal use of benzodiazepines which have repeatedly been shown to decrease the incidence of seizures when compared to placebo (12). Some controversy exists as to whether these medications should be administered on a routine or as needed (PRN) basis. The use of one benzodiazepine over another is also a subject of debate. Clonidine, various beta-blockers, and haloperidol have also been advocated. Although these agents may provide symptomatic relief, they can mask the more serious stages of AWS and should be used with caution and in conjunction with a benzodiazepine. Haloperidol may also lower the seizure threshold. Parenteral and/or enteral alcohol therapy is advocated by some although prospective randomized trials comparing this to benzodiazepine therapy do not exist. There are rare case reports regarding the use of propofol in refractory delirium tremens (6).

A brief discussion addressing the pharmacologic properties of benzodiazepines and neuroleptics follows describing the more common approaches to dealing with patients experiencing AWS. No consensus exists. A meta-analysis and evidence-based practice guideline was performed in 1997 by Mayo-Smith et al and the reader is encouraged to review this (12).

BENZODIAZEPINES

Benzodiazepines are widely used to treat patients with AWS and are considered to be the drug class of choice. They have minimal respiratory and cardiac depressant effects, are widely available, are cross tolerant with alcohol (similar use of gamma-aminobutyric acid (GABA) receptors) in the brain and offer excellent anticonvulsant activity. Anterograde amnesia is also common and beneficial. When used for

the short-term treatment of delirium, physical dependence is rare. All of the agents listed below have been used to treat and ameliorate the symptoms of AWS. The characteristics of the individual agents vary significantly (9). Although few clinically significant differences have been found, controversy exists as to the optimal benzodiazepine for treating AWS patients. Agents with long half lives may produce unwanted prolonged sedative effects, however, some argue that this property provides a smoother withdrawal and evidence suggests that these long-acting agents may be more effective in preventing seizures (20).

Prolonged sedation may, however, be cumbersome or unwanted in some patients. The method of metabolism is also important in choosing the optimal agent. Those agents metabolized by hepatic oxidation must be given with caution in the elderly and those with hepatic dysfunction. An agent with a simpler hepatic degradation process (glucuronide conjugation) may be beneficial in certain patient populations. The agent's lipophilicity is also important as more lipophilic agents enter the central nervous system more quickly and are more effective in controlling acute seizure activity. Benzodiazepines that have a rapid onset are thought to have an increased abuse potential, however, this is probably more of a concern in a less acute, outpatient setting.

DRUG	EQUIPOTENT DOSE	HALF LIFE	ONSET	TIME TO PEAK ACTION	DURATION	ACTIVE METABOLITES
Chlordiazepoxide	20 mg	5-30 hrs	Intermediate	0.5-4.0	Short	Yes t _{1/2} =5-30 hrs
Diazepam	5 mg	20-100 hrs	Very fast	0.5-2.0	Short	Yes t _{1/2} =30-200 hrs
Lorazepam	1 mg	10-20 hrs	Intermediate	1.0-6.0	Intermediate	None
Midazolam	2.5 mg	1-4 hrs	Very fast	0.5-1.0	Very short	None

CHLORDIAZEPOXIDE (Librium®): The oldest of the benzodiazepines (introduced in 1960). Largely supplanted by the newer agents as it cannot be given intramuscularly (IM) due to its slow and erratic absorption. It should be used with caution as its metabolites have long half-lives (see diazepam below) and its hepatic oxidation requires caution in patients with hepatic insufficiency.

DIAZEPAM (Valium®): A lipophilic agent with a very fast onset of action (1-5 minutes) making it attractive for the acute control of seizure activity. As with chlordiazepoxide, IM use is discouraged due to its erratic absorption. It is metabolized in the liver by hepatic microsomal oxidation producing active metabolites with long half-lives that may extend the sedative and anxiolytic effects (desmethyldiazepam, t_{1/2}= 200 hrs.). Metabolism may be impaired in the elderly and those with hepatic insufficiency.

LORAZEPAM (Ativan®): The least lipid soluble of the benzodiazepines making it a less desirable alternative for acute seizure control due to its intermediate onset of action. Attractive qualities include its intermediate half-life and its lack of active metabolites. It does not undergo hepatic oxidation making it a safer alternative in patients with significant alcoholic liver disease. It also has intrinsic anti-emetic properties that may be helpful in the postoperative patient. It may be administered sublingually.

MIDAZOLAM (Versed®): A short half-life, rapid onset, and brief duration of action together with water soluble properties make this agent suitable for continuous intravenous (IV) infusion.

HALOPERIDOL (Haldol®)

Haloperidol is a neuroleptic agent whose use in treating delirium in the critical care setting is well described, safe, and effective. It is frequently used in combination with other agents, especially the benzodiazepines. Neuroleptic agents are non-addictive with very little development of tolerance to their beneficial effects. Potential complications include extrapyramidal effects, which may be acute in onset and are not dose-related. These reactions appear to be related to oral administration of the agent and are rare with IV administration. Such reactions usually require either lowering the dose of the neuroleptic

agent or discontinuing its use altogether. These agents have also been associated with tardive dyskinesia and neuroleptic malignant syndrome (NMS).

Haloperidol may be given orally, IV or IM. For the rapid control of acute delirium, the IV route is preferred. Onset of action after an IV dose is 10-30 minutes. This agent minimally impairs respiratory and cardiovascular function, making it attractive in the unstable critically ill patient. It is a central dopamine receptor antagonist although its exact mechanism of action is unclear. Dosages depend on the degree of agitation and are typically 0.5-2 mg for mild agitation, 5mg for moderate agitation and 10-20mg for severe agitation repeated as necessary until agitation is controlled. Reports of the safe use of massive dosages of haloperidol are common. Haloperidol may be safely used concomitantly with the various benzodiazepines.

INTRAVENOUS ETHANOL

The use of intravenous ethanol in the management of AWS is controversial and practiced sporadically. Opponents to its use cite its narrow margin of safety, short duration of action, potential toxicity and drug interactions, possibility of irritation at the infusion site, the need to continuously monitor levels, the possibility for gastric irritation and its interaction with many medications. Ethical concerns also exist, although it has been stated that this form of treatment is not unlike using methadone for heroin detoxification (4). There is a lack of randomized controlled data evaluating its efficacy compared to other more conventional forms of treatment and literature on the subject provides little guidance. A few case series do exist, several of which are briefly outlined below.

LITERATURE REVIEW

Several reports demonstrate the effectiveness of benzodiazepines over placebo for the prevention of seizures and delirium. A meta-analysis by Mayo et al demonstrated a risk reduction of 7.7 seizures per 100 patients treated ($p=0.003$) and a risk reduction of 4.9 cases of delirium per 100 patients treated ($p=0.04$) (12). Benzodiazepines are the agents of choice in preventing alcohol withdrawal seizure activity (Class I). No consensus exists as to which benzodiazepine should be considered first line therapy in the surgical and trauma patient population. The majority of studies involve medical and psychiatric patients taking oral benzodiazepines. Miller et al. performed a double-blind comparison between lorazepam and diazepam in the treatment of AWS (18). There were no statistical differences between the two agents with regard to efficacy. Solomon et al completed a double-blind comparison of lorazepam and chlordiazepoxide (16). Again, no significant differences were found between the two agents. The authors in the two studies above concluded, however, that "lorazepam may have therapeutic advantages" and that "because of its simpler and more predictable metabolic pathway and its insignificant accumulation in the plasma during multiple-dose therapy, lorazepam may be the drug of choice." Ritson and Chick also compared diazepam to lorazepam in a randomized, double-blind manner (17). The lorazepam group demonstrated greater depression ($p<0.01$) and anxiety ($p<0.05$) as well as increased tachycardia ($p<0.05$). Withdrawal symptoms were significantly less in the diazepam group ($p<0.05$). The authors concluded that patients in the diazepam group had a significantly more comfortable withdrawal phase (presumably due to the extended half-life of diazepam) with improved cognitive skills (Class I).

Class II data suggests that the longer-acting benzodiazepines may be more effective in preventing withdrawal seizures (16,20). Mayo-Smith et al observed eleven seizures in 1044 admissions (1.1%) for alcohol withdrawal treated with a standardized protocol of short acting benzodiazepines (oxazepam). 82% of the seizure activity occurred 12 to 48 hours after cessation of the oxazepam. They hypothesized that the rapid fall in benzodiazepine blood levels with discontinuation of the short-acting agent contributed to the seizures. Hill et al. reported 3 cases of major seizure activity within 24 hours of completing detoxification with oxazepam (21). In another study, although not statistically significant, seizures occurred in 8% of those treated with lorazepam compared to 0% in those receiving chlordiazepoxide (16). Ritson identified a 5% seizure incidence with lorazepam compared to 0% with diazepam. Mayo-Smith et al subsequently substituted chlordiazepoxide for oxazepam and did not witness any seizure activity in the subsequent 1030 patients. Saitz et al performed a randomized double-blind controlled trial to compare the effectiveness of a standard dosing schedule of benzodiazepines vs. dosing on a PRN basis (3). Those patients treated with symptom-triggered therapy completed their courses sooner and required less

benzodiazepine. Symptom-triggered therapy was considered to be as efficacious as routine therapy as there were no significant differences between the groups with regard to CIWA-Ar scores, delirium tremens, hallucinations or seizures. Routine prophylaxis, therefore, does not appear necessary (Class I).

Craft et al. studied 37 trauma patients treated for AWS with IV ethanol (4). Patients with signs of AWS were started on a 10% EtOH in D5W (vol/vol) IV drip at 50cc/hr. Treatment was continued for 48 hours and then weaned over the next 48 hours. The average time to amelioration of symptoms was 14 hours and the duration of treatment averaged 4 days. The effectiveness of the EtOH drip was rather subjective and graded from 1 to 5 (1=poor, 5=very good). Five of the 37 patients had a poor or no response. Patients were said to have remained calm, alert, oriented and able to participate in treatment, qualities that may not be present with the potential excess sedation caused by benzodiazepines. There were no serious complications. Hansbrough et al. studied 22 alcoholic burn patients treated with IV ethanol (10). Infusions were continued for a 3-8 day period. A similar alcohol drip was started as described in the previous study. Patients studied were those "suspected" to be heavy drinkers and the authors readily admit that perhaps some of them were not. Patients did not experience clear signs of alcohol withdrawal nor did they appear sedated. DiPaula et al performed a retrospective review of their experience with IV ethanol. They stressed the need for reliable documentation with regard to the patient's past history, risk factors, and admission blood alcohol levels (BAL) in guiding which patients should receive IV ethanol therapy. They also stressed the need for serial BAL's when the patient is receiving IV ethanol therapy. They recognized the great degree of variation of ethanol-prescribing within their institution and the need to develop clear and effective guidelines. (Class II). Dissanaikie compared their results with the use of IVE before and after development of a protocol and found that protocol driven therapy decreased the failure rate of IVE therapy as well as the treatment time and concluded that IVE therapy was a viable option for AWS prophylaxis when administered in a systematic protocol (22).

A recent randomized trial was published in the Journal of Trauma comparing intravenous ethanol versus diazepam. Trauma patients admitted to the ICU with a history of chronic daily alcohol consumption of greater than or equal to five beverages per day were prospectively randomized to intravenous ethanol infusion versus scheduled-dose diazepam and were evaluated with the Riker sedation-agitation scale. The authors concluded that intravenous ethanol offered no advantage over diazepam with respect to efficacy or adverse sedative effects. (23)

Numerous small series and case reports document experience with less commonly used pharmacological agents. Perhaps the drugs most studied in this regard are the anti-epileptic drugs, namely carbamazepine. Malcolm et al compared the effects of carbamazepine and lorazepam and found that both drugs were equally efficacious at treating the symptoms of alcohol withdrawal (24). The carbamazepine group had less post-treatment relapses and a greater reduction in anxiety symptoms. This particular work studied patients treated in an out patient setting and may not be applicable to the acute symptoms of ethanol withdrawal treated in the more acute setting. Schik et al studied the use of oxcarbazepine and carbamazepine in the inpatient treatment of alcohol withdrawal (25). The oxcarbazepine group was found to have less of a "craving for alcohol." Mariani et al studied Gabapentin in the treatment of alcohol withdrawal and suggested further study (26). Myrick et al compared the anticonvulsant Tiagabine to benzodiazepines and saw equal reduction in alcohol withdrawal symptoms. (27). Addolorato et al compared Baclofen to Diazepam and although diazepam was slightly more rapid, efficacy was otherwise comparable (28). Although the numbers are small and firm recommendations cannot be made at this time, there is promise that some of these agents with less addiction potential and reduced sedative side effects could be valuable adjuncts in the future.

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