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EM CASE OF THE WEEK

BROWARD HEALTH MEDICAL CENTER DEPARTMENT OF EMERGENCY MEDICINE

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) estimates that the prevalence of alcohol dependence in the United States is 5%, but up to 3 of every 10 adults drinks alcohol at levels associated with adverse health and social consequences

EM CASE OF THE WEEK

EM Case of the Month is a monthly "pop quiz" for ED staff. The goal is to educate all ED personnel by sharing common pearls and pitfalls involving the care of ED patients. We intend on providing better patient care through better education for our nurses and staff.

Alcohol Withdrawal

A 55 year old Caucasian male with a known history of alcoholism is brought to the emergency room by his sister after complaints of nervousness and anxiety. The patient states that he decided to stop drinking alcohol "cold turkey" 2 days ago. He states he normally drinks 4 or 5 drinks of vodka daily but he has not had any alcoholic beverages since then. He has a history of atrial fibrillation, hypertension, dyslipidemia, and GERD. Vitals signs show an elevation of blood pressure, heart rate, and temperature. He appears visibly tremulous and diaphoretic but he answers questions appropriately. His physical examination is otherwise unremarkable. His lab results show a low albumin and low total protein levels and an elevated prothrombin time/partial prothrombin time value. Which benzodiazepine is the most appropriate agent for this patient's alcohol withdrawal?

A. Alprazolam

B. Diazepam

C. Lorazepam

D. Chlordiazepoxide

E. Clonazepam

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Agents NOT metabolized by the liver	Long-acting agents
Lorazepam Oxazepam Mirtazepam	Chlordiazepoxide Diazepam Chlorazepate

Pharmacokinetics of a few of the more commonly used benzodiazepines used to treat alcohol withdrawal.

Take Home Points

- Prevention of severe respiratory depression and aspiration of vomitus are the most important goals for managing acute alcohol intoxication.
- The average blood alcohol concentration in fatal cases is above 400 mg/dL, although the lethal dose varies due to tolerance.
- The treatment of choice for alcohol withdrawal is benzodiazepines with careful consideration to the pharmacokinetics of the agent selected for treatment based on the patient's liver function
- Alcohol withdrawal occurs hours to days after heavy use and can include life-threatening emergencies including seizures, delirium tremens, and the Wernicke-Korsakoff syndrome
- The CIWA scale is an objective assessment of alcohol withdrawal that can be used to guide appropriate benzodiazepine administration based on the severity of symptoms and signs.

Alcohol Withdrawal

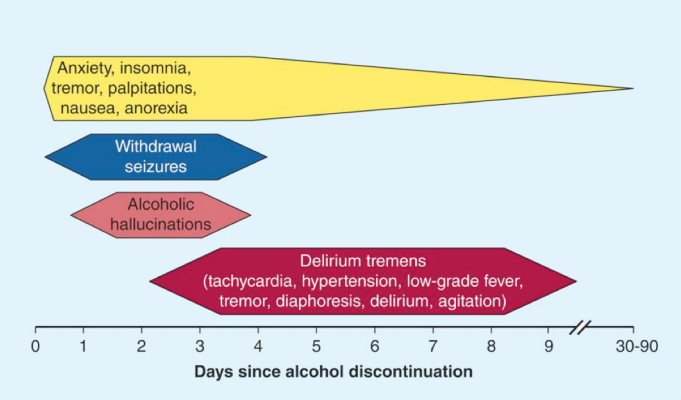
The correct answer is C. Of the choices presented, only lorazepam (Ativan) is metabolized by glucoronidation, a biochemical process that is not dependent on liver function. This patient clearly has lab values that demonstrate altered liver function. A poorly functioning liver can be demonstrated by any combination of the following: low albumin levels, low total protein levels, or an increased prothrombin time/partial prothrombin time value, amongst others. Thus, it is imperative that the benzodiazepine of choice not be metabolized by the liver. The goal of medical management of alcohol withdrawal is to ultimately prevent the occurrence of seizures, delirium, and arrhythmias. Alprazolam (Xanax) is a short acting agent and is not appropriate for alcohol withdrawal management. While they are longer acting benzodiazepines, both diazepam (Valium) and chlordiazepoxide (Librium) are significantly metabolized by the liver. In this patient, use of benzodiazepines that are metabolized by a poorly functioning liver could result in excessive drug levels in the blood, resulting in over-sedation.

Discussion

Alcohol acts as a depressant on the central nervous system by targeting both the **gamma-aminobutyric acid type A (GABA-A) receptors** and serotonin receptors, thus producing tolerance and habituation in long-term drinkers. In fact, positron emission tomographic (PET) studies have demonstrated a globally low rate of metabolic activity, particularly in the left parietal and right frontal areas in otherwise healthy person withdrawing from alcohol. Benzodiazepines and barbiturates also target GABA-A receptors, and are used for alcohol withdrawal. Understanding how these drugs are metabolized in the body is very important, especially in individuals that have a history of liver dysfunction. **Benzodiazepines** are generally favored over barbiturates for treatment of alcohol withdrawal in the emergency department as the latter has been linked to major adverse drug effects (including respiratory inhibition and sedation) at higher doses. In healthy patients, longer acting benzodiazepines are preferred due to their intrinsic tapering effect and less frequent dosing. However, in patients with altered liver function, shorter acting agents that become metabolized to inactive water-soluble metabolites are preferred. After successful management of acute alcohol withdrawal, benzodiazepines must be slowly tapered over the course of several weeks to months to achieve normal nervous system function, especially sleep. The pharmacokinetics of the most commonly used benzodiazepines is represented above.

Signs and symptoms

As represented in the graph below, abrupt cessation of alcoholic intake follows a characteristic pattern and timeline. Alcohol withdrawal starts **about 6-8 hours after the last drink** and includes anxiety, tremulousness, sweating, insomnia, palpitations, tremor, etc. These symptoms can easily be appreciated as the body clears alcohol and its subsequent depressive effects on the central nervous system. Tremor is the most characteristic sign of alcohol withdrawal yet milder forms of this list of symptoms can persist even for several months. Although not as common, patients can also experience visual hallucinations. Additionally, a **reduction in the seizure threshold** can result in the acute onset of seizures typically **24 hours after** the last alcoholic beverage. Thus, benzodiazepines reduce the symptoms of alcohol withdrawal and lower the probability of inducing a seizure. **Delirium tremens** involves autonomic system hyperactivity. Seen typically **2-7 days after alcohol cessation, it is a medical emergency with an associated increase in mortality if not recognized and treated acutely with benzodiazepines**. Symptoms are illustrated below. This life-threatening condition requires stabilization in an acute medical facility.



Source: Katzung BG, Masters SB, Trevor A. *Basic and Clinical Pharmacology*. 12th ed. New York, NY: McGraw-Hill; 2012: Figure 23-2.

Wernicke-Korsakoff syndrome

Wernicke's encephalopathy is a syndrome linked to thiamine (vitamin B1) deficiency that is composed of the triad of confusion, ophthalmoplegia, and ataxia. **Korsakoff's psychosis** includes irreversible memory loss, confabulation, and personality change. Both conditions are associated with periventricular **hemorrhages and necrosis of the mammary bodies in conjunction with thiamine deficiency** most likely as a result of poor dietary habits commonly seen in alcoholics. Intravenous thiamine is the treatment. It should be noted that administration of glucose solutions that do not contain thiamine can precipitate further neurologic injury through the oxidative metabolism of sugars. Thus, dextrose should always be co-administered with thiamine in any patient displaying signs or symptoms of the Wernicke-Korsakoff syndrome.

Further Management

Patients with acute alcohol withdrawal should be monitored with further laboratory tests. A complete blood count (CBC) and comprehensive metabolic panel (CMP) should be obtained to monitor platelet count, red blood cell levels, electrolyte levels, renal function, glucose level, and liver transaminase levels. Potassium, magnesium, and phosphate balance must be maintained depending on the patient's renal function. In alcoholics, AST levels are routinely twice that of ALT levels. Macrocytic anemia is common in alcoholics, and both folate and vitamin B12 levels should be monitored. In patients with excessive vomiting, hyperkalemia and metabolic alkalosis may occur. Potassium balance should be monitored with close observation of renal function.

Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale

The goal of the **CIWA scale** is to establish an objective and reliable assessment of alcohol withdrawal by scoring and summing ten signs/symptoms of alcohol withdrawal, including: nausea and vomiting, tremor, headache, visual disturbances, auditory disturbances, tactile disturbances, agitation, anxiety, paroxysmal sweats, and orientation and clouded sensorium. Each item is scored 0-7 (except for orientation, which is rated from 0-4). The maximum score possible is 67, with mild withdrawal defined as a score from 0-15, moderate withdrawal as 16-20, and severe withdrawal any score greater than 20. This scale guides benzodiazepine administration.

ABOUT THE AUTHOR:
This month's case was written by Marc Ciesco. Marc is a 4th year medical student from NSU-COM. He did his emergency medicine rotation at Broward Health North in April 2015. Marc recently matched at the Medical College of Georgia in Augusta, GA in Internal Medicine for his residency.