Disulfiram and Hypotension in a 53-year-old Woman

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ABSTRACT
We describe a case of disulfiram-ethanol reaction in a patient presenting with altered mental status. The patient was found to be profoundly hypotensive, requiring multiple vasopressor agents. As the symptoms associated with disulfiram reaction are non-specific, it is important to maintain a high level of suspicion for drug reaction when caring for the undifferentiated altered and hypotensive patient.

KEYWORDS: disulfiram-reaction, alcohol-dependence, altered mental status, hypotension

CASE REPORT
A 53-year-old woman with a history of alcohol dependence and bipolar disorder, currently prescribed diazepam, lithium, trazodone, zolpidem, disulfiram, and propranolol, was found by her family on the floor of her home, surrounded by pills and beer cans. She presented to the hospital with altered mental status.

On arrival to the hospital, the patient was obtunded and hypotensive. Her vital signs demonstrated blood pressure of 75/40 mmHg, heart rate of 87 beats per minute, respiratory rate of 16 breaths per minute, SpO₂ of 95% on room air, and a temperature of 98.1°F. Her pupils measured 4 mm and were reactive. She had moist mucous membranes. Her neck was non-tender and without signs of meningismus. The patient had clear lung fields and had an unremarkable cardiac examination. Her abdomen was soft, non-tender, and non-distended. Neurologic exam revealed an obtunded patient with spontaneous eye opening and incomprehensible speech. There was no clonus. The patient was somnolent, unable to follow commands but responded appropriately to noxious stimuli and was able to move all four extremities equally. Her skin examination was significant for diffuse erythema across her face, chest, and upper back.

An ECG revealed a sinus rhythm at a rate of 90, with normal intervals and without significant ST elevations or depressions. Her laboratory evaluation revealed an elevated blood alcohol level of 148 mg/DL and a lactate level of 2.7 mEQ/L. A lithium level was non-detected. A urine screen for drugs of abuse tested positive only for benzodiazepines. She remained persistently hypotensive after fluid resuscitation, and required vasopressor support with norepinephrine and vasopressin. The patient’s presentation and physical examination did not clearly fit a single toxidrome such as serotonin syndrome, nor an overdose of a beta-blocker or an opiate. Based on her medication list, blood alcohol level, flushing, and hypotension, she was admitted to the Medical Intensive Care Unit with a presumptive diagnosis of a disulfiram-ethanol reaction.

DISCUSSION
History
The history of disulfiram and its introduction to medical therapy resulted from the accidental intersection of industry and medicine. Disulfiram, or Antabuse [tetra-ethylthiuram disulfide], is a drug approved [in the US] for the treatment of alcohol addiction. Disulfiram has been used since the 1800s in the rubber manufacturing industry, in a rubber stabilization process known as vulcanization. In the 1930s, an American physician, E.E. Williams, noted that a group of workers exposed to disulfiram at a chemical plant became symptomatic after drinking alcohol.

After a glass of beer (6 ounces) the blood pressure falls about 10 points, the pulse is slightly accelerated, and skin becomes flushed in the face and wrists. In fifteen minutes the blood pressure falls another 10 points, the heart is more rapid, and the patient complains of fullness in the head. There doesn’t seem to be any other effect of the chemical; men have worked here for years without any complaint other than their inability to drink. They have become involuntary total abstainers...If the chemical compound is not harmful to man, one wonders whether one has discovered the cure for alcoholism.

Dr. Williams postulated that disulfiram could be used to treat alcoholism. About a decade later, in late 1940s, two Danish researchers, Hald and Jacobsen, arrived at the same conclusion while researching disulfiram as an anti-helminthic after Jacobsen, a physician with a penchant for self-experimentation, sampled the medication and experienced the same adverse reaction after drinking alcohol. They teamed up with a physician, Martensen-Larnsen, to perform clinical trials and found disulfiram to be an effective...
Mechanism of Aversion
Disulfiram does not have any central nervous symptoms effects to decrease alcohol cravings. Instead, its administration is intended to deter alcohol consumption by causing the patient to fear the unpleasant and serious reaction that follows alcohol intake while on the drug. In reality, rather than not drinking, many patients struggle with compliance and do not take disulfiram on a regular basis. In fact, adherence rates have been found to be as low as 20%.

Mechanism of Action and Symptoms
The adverse disulfiram-ethanol reaction is due to acetaldehyde. The first step of ethanol metabolism is the conversion of ethanol to the intermediate, acetaldehyde, by alcohol dehydrogenase. Acetaldehyde is subsequently broken down to acetate by aldehyde dehydrogenase. Disulfiram and its metabolites prevent this pathway from running to completion by irreversibly inhibiting aldehyde dehydrogenase, leading to a 5 to 10-fold increase in acetaldehyde concentration.

Within minutes, the increased acetaldehyde concentration results in adverse symptoms. Many of these symptoms are due to the acetaldehyde-mediated release of histamine. The symptoms of this response ranged from mild reactions including facial flushing, sweating, and a headache to moderate reactions including to nausea and vomiting. More severe reactions are characterized by significant hypotension and tachycardia. In the most severe reactions, arrhythmias, cardiovascular collapse, seizures, and death can also occur.

The profound hypotension seen in the disulfiram-ethanol reaction is not only due to histamine release, but is also mediated by direct inhibition of dopamine-beta hydroxylase (DBH) by disulfiram and its metabolites. As DBH synthesizes norepinephrine from dopamine, inhibition by disulfiram results in depletion of endogenous norepinephrine. In addition, acetaldehyde has been observed to have a direct vasodilatory effect in the setting of norepinephrine depletion.

Causes of Disulfiram Reaction
The disulfiram-ethanol reaction can occur with exposure to alcohol from any route. While consumption of alcohol [often intentional] is the most common cause of the reaction, many common – and some unexpected – items contain alcohol. Household products such as adhesive, detergents, foods [liquor-containing desserts, fermented vegetables, vinegars, and sauces], various medications, toiletries such as after-shave, cologne, deodorants, contact lens solution, as well as many cleaning supplies and industrial products may all contain alcohols in various forms. From beer-containing shampoos to kitchen cleaning products, libations are among many possible routes to alcohol exposure.

In addition to alcohol, many medications can interact with alcohol to cause disulfiram-like reactions. While the mechanisms of these reactions have not been fully elucidated in some cases, common examples include metronidazole, cephalosporins, sulfamethoxazole/trimethoprim, sulfonylureas, certain HIV/HAART therapy drugs such as abacavir, and various fungicides.

Another substance that causes a disulfiram-like reaction is the inky cap or shaggy mane mushroom (Coprinopsis atramentaria). The mushroom gets its name from its release of inky liquid once picked, caused by release of a peptidase which auto-digests the gills. The mushroom contains the toxin coprine. The metabolites of coprine, similar to disulfiram, inhibit aldehyde dehydrogenase and cause an increased concentration of acetaldehyde and subsequent disulfiram-like reaction upon concurrent exposure to alcohol.

Treatment
In the case of a disulfiram-ethanol reaction or a disulfiram-like reaction, the treatment is the same and consists of supportive care. GI decontamination is not recommended. In the setting of vomiting, diaphoresis, and hypotension, IV fluid resuscitation is recommended. Anti-emetics and histamine-antagonists can treat many of the histamine-mediated symptoms. In severe reactions with profound hypotension, norepinephrine is the vasopressor of choice given the blockade of endogenous production of the catecholamine.

Advanced Therapy
Case reports describe the use of fomepizole in refractory cases. The antidote for volatile alcohol poisoning, fomepizole, is a competitive inhibitor of alcohol dehydrogenase, which prevents the production of acetaldehyde and has been anecdotally shown to rapidly improve symptoms in severe reactions. In life-threatening circumstances, hemodialysis to remove the alcohol substrate has also been suggested as a possible treatment.

SUMMARY AND CASE RESOLUTION
The symptoms associated with a disulfiram-ethanol reaction are non-specific. Taken out of context, or in scenarios where minimal history is available, it is easy to overlook disulfiram as the culprit. Case reports describe encounters...
in which disulfiram-ethanol reactions were misdiagnosed as ACS, cardiogenic, anaphylactic, and septic shock.\textsuperscript{12-14} In the case initially described, the patient’s presentation was highly suggestive of a poly-ingestion, with suspicion for a disulfiram-ethanol reaction based upon her medication list, blood alcohol level, vital signs, and physical examination. She was treated with IV fluids and ultimately required multiple vasopressors for blood pressure support. She gradually improved over hours and was transferred to inpatient psychiatry once medically stable. Her disulfiram was discontinued.

References

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