Delirium-Associated Disulfiram and Ethanol Interactions

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Background: Disulfiram, an agent used for the treatment of alcohol dependence, can exacerbate psychiatric syndromes (including psychosis, catatonia, delirium, depression, and mania) after extended use. However, delirium has yet to be reported following the short-term use of disulfiram in the setting of alcohol use.

Objectives: We report a case with a neuropsychiatric presentation and discuss the prevention and the progression of delirium associated with an interaction of disulfiram and ethanol.

Case Report: We report the case of a 51-year-old woman who developed disorganized speech, diminished communication, a decrease in appetite, and thoughts of suicide 10 days after she began taking disulfiram (250 mg/day), to which she added 1 glass of alcoholic beverage for 2 days. Delirium developed in association with an interaction between disulfiram and alcohol. The patient met DSM-IV criteria for major depressive disorder, alcohol dependence, and delirium.

Discussion: Neuropsychiatric manifestations may develop in association with co-administration of disulfiram and alcohol; timely recognition and treatment are recommended.

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Disulfiram, an agent used for the treatment of alcohol dependence for nearly 60 years, can induce a variety of neuropsychiatric manifestations (e.g., paranoia, impaired memory, decreased concentration, depression, ataxia, dysarthria, and frontal release signs [such as snout and grasp reflexes]).[1–7] In addition, hepatotoxicity and fatigue have also been associated with disulfiram use.[7]

Adverse reactions (involving headache, flushing, nausea, vomiting, diaphoresis, tachycardia, hypotension, and confusion) may arise when alcohol is ingested during extended use of disulfiram.[2] These effects are the result of an autonomic symptom complex caused by an accumulation of acetaldehyde (due to disulfiram's inhibition of aldehyde dehydrogenase), which in turn causes the release of histamine.[2,3,7–9]

To the best of our knowledge, delirium has yet to be reported following the short-term use of disulfiram in the setting of alcohol use. We report such a case, discuss the reasons why it might occur, and offer treatment strategies.

CASE REPORT

Ms. A, a 51-year-old woman, presented at the Emergency Department (ED) with 3 days of decreased appetite, disorganized speech, diminished communication, and thoughts of suicide. Ms. A's family said that she seemed both anxious and frightened; she kept repeating "I want my husbands," and was often nonresponsive to questions or comments. Ten days earlier she began taking disulfiram (250 mg/day); in addition, she drank 1 glass of an alcoholic beverage for the past 2 days. Her psychiatric history was notable for major depressive disorder (lasting 3 months) and alcohol dependence (for 5 years) based on DSM-IV criteria. However, she had never required an inpatient psychiatric admission.

On arrival at the ED, she was intermittently oriented to person, but disoriented to time and place. Her speech alternated between shouting and muttering. Her affect was irritable and anxious, and she was intermittently agitated. She appeared to have thought blocking and impaired attention; she did not reveal paranoia, ideas of reference, or delusions.

Her medical history included hypertension and a childhood history of head trauma (without sequelae). Ms. A had no history of delirium tremens, seizures, or alcoholic hallucinosis.

On physical examination, she was afebrile and normotensive. She was hyperreflexic bilaterally. An electrocardiogram showed sinus tachycardia (heart rate of 120 beats/min) and elevated serum transaminase levels. An electroencephalogram (EEG) revealed diffuse slowing and hyperexcitability in frontal and right occipital re-

gions. A magnetic resonance imaging showed evidence of childhood head trauma, i.e., contusion in the left temporal region. The results of other tests (e.g., serum electrolytes and complete blood count) were normal.

The patient currently met DSM-IV criteria for major depressive disorder, alcohol dependence, and delirium. Ms. A was given haloperidol (10 mg/day intravenously for 7 days); then, she was given risperidone (2 mg/day for 4 days). Vitamin B complex was administered intravenously, and topirimate was started to prevent seizures. Verapamil was started to control Ms. A's tachycardia. Her tachycardia was normalized after 2 days and elevated transaminase levels were normalized after 5 days. Ms. A's confusion and agitation diminished after the first week, and these symptoms disappeared completely by the end of the second week. She was oriented to place and person on the seventh hospital day, at which time a repeat EEG showed no abnormality. During the third week of her hospital stay, fluoxetine (20 mg/day) was started to treat an underlying depression.

DISCUSSION

Disulfiram-associated encephalopathy, although uncommon, typically occurs within the first few months of disulfiram therapy.[2,3] Our patient, Ms. A, developed disulfiram encephalopathy (delirium) after taking disulfiram for only several days. We suspect that this syndrome may also have been exacerbated by the concomitant use of alcohol, causing a disulfiram-ethanol reaction.

Abnormally high (circulating and tissue) concentrations of acetaldehyde, disulfiram itself, and major metabolites diethyldithiocarbamate (DDC) and carbon disulfide often provoke side effects.[10] New evidence has shown that both intoxication and low, single doses of disulfiram and DDC increase extracellular levels of striatal glutamate, an excitatory neurotransmitter that can have neurotoxic effects when released in excess of physiologic concentrations.[11–13] Disulfiram, and to a much lesser extent DDC, also provokes [^{3}H]-dopamine loss (via a moderate increase in membrane permeability and a detergent-like effect), which might represent a nonspecific component in the thiol-evoked vesicular glutamate release.[14] A prolonged (0.7 hr) increase in glutamate release related to acute disulfiram intoxication (that is associated with the heterogeneous neurotransmitter impairment linked with nonselective thiols) might contribute to lesions in the basal ganglia.[10] Since the metabolism of acetaldehyde also involves the formation of cytotoxic free radicals, these radicals may affect cerebral metabolism and signaling.[9] Acetaldehyde interacts with proteins that involve the hepatocyte cytoskeleton and impedes membrane transport[15]; this may explain Ms. A's initially elevated transaminase levels.

Psychosis may be induced by disulfiram's metabolite, DDC, which causes inhibition of dopamine-β-hydroxylase and leads to an increased dopamine concentration in the mesolimbic system.[16,17] Liddon and Satran[18] categorized 3 psychotic reactions secondary to disulfiram on the basis of 50 cases. The first 2 groups (35 patients) had prominent signs of delirium; half of these patients had a clear consciousness. Although delirium usually accompanies psychoses induced by disulfiram, psychosis in the presence of a clear consciousness has been reported.[7,9] Our patient showed delirium without psychosis; her symptoms resolved as acetaldehyde levels decreased. However, in some individuals, the effects of a single dose of disulfiram can last up to 2 weeks.[19]

Unfortunately, between 25% and 50% of alcoholics drink while taking disulfiram.[20,21] Mueser and coworkers[22] found that most of their disulfiram-treated patients (76%) used alcohol. Despite this, only a minority (28%) who used alcohol reported adverse reactions, the most common of which were vomiting and a flushed face.[22] Similar to the findings of Liskow and associates,[20] most patients who experienced a reaction to alcohol while taking disulfiram did not seek treatment. They also reported nonstatistically significant increases in anxiety and depression, while paranoia/delusions decreased and increased in equal numbers, and hallucinations and agitation were uncommon.

Fortunately, there is considerably less of a disulfiram-ethanol reaction (DER) with the 250-mg dose than with a 500-mg dose of disulfiram.[1] Moreover, 250 to 500-mg doses are insufficient to cause a DER in some patients.[23] Adverse reactions to alcohol and disulfiram in our patient may not have been related to the dosage of disulfiram, its usage, or the amount of alcohol ingested.

Implications for Clinical Care

Prevention. Some clinical reports[18,24–26] suggest that disulfiram can exacerbate psychiatric syndromes (e.g., psychosis, catatonia, delirium, depression, and mania); these reports contribute to a general reluctance on the part of practitioners to prescribe disulfiram to persons with severe mental illness.[20] Supervised disulfiram treatment in persons with severe mental illness and alcoholism can lead to positive results,[27] although this was not true for our patient. Unfortunately, our patient met DSM-IV criteria for major depressive disorder, alcohol dependence, and delirium; however, her psychiatric symptoms arose during disulfiram therapy. We suggest that patients with dual diagnoses not receive disulfiram as a first-line treatment for alcoholism. Huffman and Stern[19] also indicated that disulfiram should be avoided in patients with a history of dangerous impulsive behavior or with a high risk for suicide.

Recognition. In a patient with an acute change in mental status during disulfiram therapy, the differential diag-

nosis should include delirium caused by use of disulfiram and its metabolites as well as a DER.

Management. A selective serotonin inhibitor, fluoxetine, was started to control Ms. A's depression. Thase and colleagues,[28] in their review of the treatment of depression in alcoholics, discuss disulfiram as a treatment for alcohol dependence and endorse the use of selective serotonin reuptake inhibitors, but they did not report whether the combination has been safely used. On the basis of disulfiram's potential to lower epileptic threshold,[19] topiramate was started.

Neuropsychiatric manifestations may develop in association with coadministration of disulfiram and alcohol; timely recognition and treatment of the manifestations of such interactions are recommended.

Drug names: disulfiram (Antabuse), fluoxetine (Prozac and others), haloperidol (Haldol and others), risperidone (Risperdal), topiramate (Topamax), verapamil (Tarka, Verelan, and others).

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