High-dose Disulfiram-induced Delirium and Manic Features: A Case Report

Disulfiram is an aldehyde dehydrogenase inhibitor that affects the metabolism of alcohol, increasing blood acetaldehyde level to treat alcohol use disorder. Disulfiram is also known to be a dopamine-β-hydroxylase (DBH) inhibitor with potential to cause neuropsychiatric symptoms. Manic symptoms accompanied by delirium related to disulfiram are rarely reported. Here, we present a case of a patient with alcohol use disorder, who developed acute delirium and manic symptoms after receiving a high dose of disulfiram. Those neuropsychiatric symptoms were resolved gradually as discontinuation of disulfiram.

Case Report

A 56-year-old female patient had a history of alcohol use disorder. She started to have excessive alcohol consumption after divorce eight years ago. She usually took 7–8 standard units of alcohol per day (30% volume concentration, 300–400 mL/day). She spent most time in drinking and quit her job because of drinking problem. She had all symptoms of *DSM-5* criteria of alcohol use disorder such as tolerance, withdrawal, and craving. Her first treatment of alcohol use disorder started five years ago due to unsuccessful efforts to cut down alcohol use on her own. Except for alcohol use disorder, she also had chronic depressive symptoms and was diagnosed with persistent depressive disorder. She had received selective serotonin reuptake inhibitor (SSRI) treatment as escitalopram 10 mg/day for about three years previously. She had a history of peptic ulcer but no other medical illness. Because of several times of relapsed drinking, disulfiram 200 mg/day was administrated for total abstinence. The patient took disulfiram and benzodiazepines as lorazepam 8 mg/day for the treatment of alcohol use disorder and did not drink alcohol for seven months. But she started to take higher dose of disulfiram, which was up to 1,500 mg every day since one week before the indexed admission, due to its sedative effect. One week later, she became disoriented, being brought to the emergency department, and was hospitalized for delirium.

The patient received comprehensive workups for delirium, including brain computed tomography, electroencephalography, electrocardiography, blood tests, as well as physical and detailed neurological examination, but all results were negative. Her laboratory examinations including blood alcohol concentration had no remarkable findings (glutamic-oxaloacetic transaminase, 42 U/L; glutamic-pyruvic transaminase, 40 U/L; gamma-glutamyltransferase, 53 U/L; ammonia, 73 μg/dL; and blood alcohol level, <10 mg/dL). Brain computed tomography showed no evidence of organic lesion. Delirious symptoms were improved gradually within the next three days after stopping disulfiram use, without any further treatment for delirium. But she developed manic symptoms including elated mood, racing thoughts, grandiosity, talkativeness, and decreased need of sleep. Manic symptoms were resolved within one month under treatment of carbamazepine 600 mg/day. We prescribed carbamazepine as mood stabilizer because she was worried about gaining weight. Carbamazepine is associated with a lower risk of weight gain compared with lithium and valproic acid [1]. After being discharged, she decided not to take disulfiram and had several bouts of relapses thereafter, but no further delirium and manic symptoms recurred.

Comment

We proposed that our patient's delirium and manic symptoms were related to a higher-than-normal dose of disulfiram because of the time sequence of symptoms. The possibility of alcohol withdrawal delirium was low because the patient did not take any alcohol and maintain the dosage of disulfiram as 200 mg/day for seven months. Discontinuation of disulfiram upon admission with rapid response to short-term mood stabilizer suggests that those neuropsychiatric symptoms were secondary to disulfiram misuse.

Disulfiram is known to be an inhibitor of DBH, which blocks the production of norepinephrine from dopamine, thereby causing dopamine accumulation. Many reports suggest that disulfiram may provoke psychotic symptoms or delirium through DBH inhibition [2]. Another possible pathophysiology of disulfiram-induced neuropsychiatric symptoms is the neurotoxicity due to its metabolites such as diethyldithiocarbamate (DDC) and carbon disulfide [3]. DDC can also cause the inhibition of DBH and induce psychotic symptoms, and it has also shown to block glutamate binding to receptors, further causing glutamate dysregulation [4]. Previous studies were found that even chronic administration of low doses of disulfiram can increase the extracellular level of striatal glutamate, leading to glutamate-induced neurotoxicity [3, 5]. Augmented dopamine accumulation and glutamate dysregulation can conjointly cause dysfunction in brain activity such as delirium. Although disulfiram alone is relatively nontoxic, a high-dose disulfiram may increase its metabolite, resulting in aggravating toxic effect and increased risk of neuropsychiatric symptoms.

It has been reported that disulfiram and its interaction [3, 6] with other drugs, including alcohol, may cause bipolar disorder [6-9]. Disulfiram in excess of 500 mg/day can carry a high risk of inducing mood disorder [10]. The blocked norepinephrine synthesis and dopamine-accumulating

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effect through inhibiting of DBH with disulfiram may explain the development of manic symptoms. Disulfiram-related psychiatric complications are more prevalent in certain individuals, including those with a history of psychosis, bipolar disorder, psychostimulant abuse, old age, impaired liver function, concurrent dopaminergic medications, and overly rapid increase in dosage or greater than recommended total dosage, especially in patients from Eastern countries [6, 11]. Genetic mechanism such as DBH polymorphism may offer an additional explanation for the pathogenesis of our patients [12].

As shown in the finding in our patient, the toxicity was obviously to be dose-related, while the dosage used today is relatively safe to most patients. The effective standard maintenance dose of disulfiram is ranged from 125 to 500 mg/day. In addition, previous studies suggested that disulfiram should be used at the lowest effective dose and cautioned that it should be taken when prescribing disulfiram for patients with personal and familial antecedents of psychosis [13]. Patients taking disulfiram also require to be monitored for symptoms and signs such as hepatitis, sedation, and fatigue. Baseline liver function test must be carried out as well both before and after the prescription of disulfiram [14] because disulfiram-induced hepatotoxicity is mostly categorized as idiosyncratic [15] and hepatocellular [16].

In summary, clinicians should be aware of the neuropsychiatric symptoms and its common side effect while prescribing disulfiram higher than excess of 500 mg/day [17]. (The institutional review board at Taoyuan Psychiatric Hospital, Ministry of Health and Welfare, approved this case report for publication (protocol number = R20191120, and date of approval = November 23, 2019) without any stipulation of obtaining any signed formal consent from the patient.)

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Conflicts of Interest

All authors declare no conflicts of interest in writing this report.

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