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Disulfiram Induced Psychosis: A Case Report

D. R. Survilaitė*
R. Žemaitytė**

**Republican Vilnius Psychiatric Hospital, Lithuania*

***Faculty of Medicine, Vilnius University, Lithuania*

Summary. *Introduction.* Disulfiram is one of three medications approved by the Federal Drug Administration (FDA) to treat alcohol dependence. Patients tend to abstain from alcohol to avoid the unpleasant effects of alcohol toxicity. There may be some side effects, the most common of which are drowsiness, unusual tiredness, headache, metallic taste in mouth, skin rashes, decreased libido. Disulfiram induced psychosis is a psychiatric side effect that occurs very rarely.

Case report. We report the case of a 33-year-old patient with nearly 15 years history of psychiatric personality disorder and alcohol dependence. After approximately 4 days of alcohol abstinence, as an inpatient, he was administered disulfiram. After two weeks, the patient began to feel some side effects. He was admitted to hospital and was diagnosed with disulfiram induced psychosis.

Discussion. The effect of disulfiram on alcohol metabolism was noticed in the 1940s. It should be used only by motivated patients who must be fully informed about the alcohol-disulfiram reaction. Disulfiram should only be started after about 10 days of sobriety, and the recommended dosage is 500 mg/day. The drug should be used with caution in people with a history of heart disease, diabetes mellitus, hypothyroidism, cerebral damage, nephritis, liver cirrhosis, epilepsy. Caution is recommended for patients who use benzodiazepines, some antibiotics, anticoagulants, tricyclic antidepressants. There may be some adverse effects, more serious ones include changes in vision, numbness, pain or weakness in the limbs, liver cell damage, peripheral neuropathy, seizures – but these are considered to be very rare. Psychiatric side effects may include mood changes, psychotic reactions, memory impairment. Reliable data is lacking, but cases of disulfiram induced psychosis are considered to be rare. Patients taking disulfiram should be monitored carefully.

Keywords: alcohol dependence, addiction treatment, disulfiram, side effects, disulfiram induced psychosis.

INTRODUCTION

Disulfiram induced psychosis is a rare psychiatric adverse effect of the drug disulfiram used to treat alcohol dependence. The present case is only the second instance of disulfiram induced psychosis observed by one of the authors during 52 years professional experience as a psychiatrist in a psychiatric hospital: the first one was reported in a medical journal after 28 years of work [1].

Address:
Danguolė Regina Survilaitė
Republican Vilnius Psychiatric Hospital
Parko St. 21, LT-11205 Vilnius, Lithuania
E-mail: drsurvilaite@gmail.com

Disulfiram (chemical formula $C_{10}H_{20}N_2S_4$) is usually prescribed by a psychiatrist or family doctor. Disulfiram can be found under different brand names in different countries, for example, Esperal in Lithuania, Antabuse in the USA, Antalcol, Anticol in Eastern Europe, Alcoford, Firadel, Antawell, Tyfusin, Cronotol, Dizone in India [2, 3]. The mechanism of action interferes with alcohol metabolism, by inhibition aldehyde dehydrogenase (ALDH) resulting in high blood levels of acetaldehyde, which is much more toxic than ethanol. When mixed with alcohol, disulfiram causes an acute toxic disulfiram-alcohol physical reaction which usually begins about 10 to 30 minutes after ingestion of alcohol. Sweating, flushing, respiratory difficulty, blurred vision, head and neck throbbing, nausea, vomiting, chest pain, tachycardia, vertigo, syncope, confusion can occur [4].

CASE REPORT

A 33-year-old man presented with acute psychosis and was admitted to the emergency department of the Republican Vilnius Psychiatric Hospital. The patient had existing family history of psychiatric disorders: his sister was diagnosed with F41.2 (Mixed anxiety and depressive disorder) according to the ICD-10 (International Classification of the Diseases-10), and the patient's father suffered from alcohol addiction in his 40s but managed to stop drinking after 10 years. The information that both parents of the patient were suffering from depression was found in the medical documents, the mother confirmed current use of antidepressants.

Rhesus factor incompatibility occurred during the mother's pregnancy with our patient. He was born prematurely at 36 weeks, suffered from severe newborn jaundice, and required an exchange blood transfusion. Later psychomotor development was normal. According to the parents, their son had behavioral difficulties from a young age, there were many problems with his behavior at school. He graduated from secondary school and then completed a training program as a decorator (construction worker). After studies, he worked in different countries for short periods in various construction jobs. Unwillingly, the patient confirmed our assumption, that he was fired from most of his jobs because of alcohol use. He was never married, had one child. During his lifetime, he had several encounters with law enforcement, including drunk driving.

The patient tasted alcohol when he was 11 years old at a school dance. At the age of 14, he was strongly intoxicated. Then he started drinking almost every weekend, usually a few liters of beer and 0.3 liters of vodka. At the age of 18, the patient started to drink about 5 liters of beer every weekend. The patient states, that he started to drink excessively about 8 years ago, at that time he used to drink for a few weeks, followed by about a month of abstinence. The severe hangovers started about 6 years ago. The patient was treated in our psychiatric hospital for 8 days 4 years ago. He was then admitted to the emergency room after telling his family members that he was going to commit suicide while he was intoxicated. During the psychological evaluation, the patient's personality was described as egocentric, lacking empathy and having unstable interpersonal relationships. He was considered to be impulsive, lacking impulse control, unable to control his emotion and behavior. He was diagnosed with F60.3 Emotionally unstable personality disorder, acute alcoholic intoxication, alcoholic dependence and withdrawal state. Treatment included intravenous fluids, benzodiazepines, neuroleptics. After the treatment Minnesota program and/or Alcoholics Anonymous were recommended for continued treatment support. The patient did not try either.

Although the patient claims the opposite, according to his current girlfriend, during the period of last year he started to drink alcohol even more excessively, the drinking period usually lasts from Friday to Wednesday, when he drinks approximately one liter of 40% strength alcoholic beverages per day.

The last drinking episode lasted 7 days, at the end of which he stopped for 4 days and signed into a private clinic, where he was administered Antalcol (disulfiram) at the dose of 500 mg once a day. After taking 14 tablets, the patient experienced dizziness, difficulty concentrating, numbness, tingling, pain in his arms and legs. After 20 days, he visited a psychiatrist who recommended stopping disulfiram and prescribed bromazepam. Despite the recommendation, the patient continued using disulfiram. After taking 37 tablets of disulfiram, he became fearful, suspicious, afraid to be alone, emotionally unstable. He was brought to hospital's emergency room, yet after a psychiatric evaluation was released home. Over the next 2 days at home, his condition worsened, he became disoriented, irritable, did not sleep for two nights. Then he began to see his dead relatives, hear their voices, it seemed to him that his sister was in the room, although she was in another city. Due to this, he was taken to the hospital emergency again and hospitalized.

Psychiatric status

In the emergency room, the patient was anxious, rude, and could not explain how he felt. He was disoriented in place and time. He claimed to see journalists through the hospital window (they were not there), and his behavior indicated auditory hallucinations. The patient's thinking was disturbed, it was inconsistent, we also suspected a symptom of thought broadcasting. He was dysphoric, lacked impulse control, claimed he did not understand why he was brought to the hospital. He was hospitalized involuntary and diagnosed with F29 Unspecified psychosis, according to the ICD-10.

The next day, the patient was distrustful, tense, explained that he heard his father's voice, but agreed to sign an informed consent for treatment. During the next few days, he was anxious, hostile, broke the doors of the ward, tried to escape, physical restraint had to be used for a few hours. There were almost no positive changes in psychopathology, and preparations for electroconvulsive therapy were begun. After haloperidol injection, dysphagia occurred, then haloperidol treatment was changed to oral olanzapine.

After 12 days he was transferred to another department. The symptoms of psychosis disappeared. The patient was still a little slow, easily distracted, but his thinking was quite coherent. We assessed this psychosis as disulfiram induced. He was discharged from the hospital after 26 days with the diagnosis of F06.8 Other specified mental disorders due to known physiological condition.

Treatment: injections of haloperidol (up to 10 mg/day), olanzapine (up to 20 mg/day), diazepam (up to 50 mg/day), levomepromazine (up to 50 mg/day), trihexyphenidyl (up to 4 mg/day), vitamin B complex.

Catamnesis after 2 months: the patient remains sober from alcohol, feels well, continues recommended treatment with quetiapine 50 mg/day and carbamazepine 400 mg/day.

DISCUSSION

The invention of the drug

The connection between disulfiram and alcohol consumption was first noticed at the beginning of the 20th century. Disulfiram was used in the rubber industry to accelerate the vulcanization of rubbers, both natural and synthetic products, such as neoprene. It was noticed that workers in rubber factories processing tetraethylthiuram monosulfide and disulfide had problems drinking alcohol. In 1940s, two British doctors concluded that tetraethylthiuram monosulfide was a promising drug against scabies. A few years later, two Danish scientists E. Jacobsen and J. Hald realized that the scabicide effect of disulfiram was due to its ability to absorb copper and form chelates with the metal. Experiments on rabbits confirmed their hypothesis that disulfiram was also effective against intestinal worms, which was a widespread problem at that time. Later, E. Jacobsen decided to evaluate the possible side effects on himself and after a few days confirmed that disulfiram indeed decreased the ability to ingest alcohol [5].

Administration of the drug

Disulfiram is only available by oral administration. Each oral tablet usually contains 500 mg of disulfiram. Before taking disulfiram, the patient should abstain from alcohol for at least 12 hours (according to other sources, at least 24 hours) and/or have a zero blood alcohol level [3, 4]. It is recommended to take 1 tablet (500 mg) of disulfiram for the first three days, then 0.5 tablet (250 mg) for two days, and then continue treatment taking 0.5 tablet (250 mg), 0.25 tablet (125 mg) or 1 tablet (500 mg), as needed [6]. Disulfiram does not reduce the desire to drink alcohol, but it may help in motivating the patient not to drink. For this reason, it is important to carefully select appropriate candidates for treatment: most suitable are those who have undergone detox or are committed to abstinence and receive adequate supervision.

Disulfiram should be used with caution in people with a history of cardiac disease, diabetes mellitus, hypothyroidism, cerebral damage, nephritis, hepatic cirrhosis, epilepsy. According to the official recommendations of the Republican Centre of Addictive Disorders in Lithuania, disulfiram is contraindicated in patients with severe myocardial disease or coronary occlusion, hypertension, with a history of stroke. It is also important to evaluate psychiatric condition, as it is stated that disulfiram is contraindicated in psychotic patients and those who have severe personality disorder. According to one US study, stable patients with psychotic disorders (schizophrenia spectrum) can receive disulfiram if they meet other treatment criteria. No significant psychiatric complications were reported in this group, and 64% of patients had a remission of alcoholism for at least one year [7]. The risk to the fetus is unknown, and pregnant and nursing mothers should not receive disulfiram [4, 6].

Disulfiram should be administered with caution when the patient uses the following groups of medications listed in the Table.

Possible adverse effects

The most common side effects of disulfiram include drowsiness, unusual tiredness, headache, metallic taste in the mouth, skin rashes, decreased libido. These side effects do not usually require medical attention. More serious side effects include changes in vision, mood or mental changes, numbness, pain, tingling or weakness in the hands or feet. Rarely, dark urine and severe abdominal pain may occur. About 0.1% of disulfiram-takers may suffer from liver cell damage and hepatitis. Liver toxicity, including liver failure leading to transplantation or death, has been reported, 1 in 30 000 suffer from disulfiram-induced fatal hepatitis [8]. Peripheral neuropathy, seizures and optic neuritis may also occur, these effects are usually dose-related and are considered to be very rare (less than 0.1%). Psychiatric complications appear to be more common with the use of disulfiram in India than in Western countries. Psychiatric ad-

Table. **Drug interactions with disulfiram and their management** [4]

Drug	Effect with disulfiram	Recommended action
Benzodiazepines	Decreases plasma clearance of diazepam	Substitute lorazepam
Isoniazid	May cause unsteady gait, changes in mental state	Discontinue disulfiram if either effect is noted
Rifampicin	If used with isoniazid to treat tuberculosis, see isoniazid effects above	Adjust dosages as needed
Metronidazole	Leads to greater risk of confusion or psychosis	Do not prescribe disulfiram and metronidazole together
Oral anticoagulant	Inhibits anticoagulant metabolism	Adjust dosages
Oral hypoglycemic	Produces disulfiram-like reactions with alcohol	Monitor carefully
Phenytoin	Increases serum levels	Reevaluate and adjust doses
Theophyline	Increases serum levels	Reevaluate and adjust doses
Tricyclic antidepressants	May cause delirium	Adjust dosages, discontinue disulfiram or switch to another class
Desipramine, imipramine	Decreases total body clearance and increases elimination half-life levels	Monitor closely, adjust dosages if needed

verse effects might include psychotic reactions, depression, paranoia, mania, personality changes, memory impairment; there have even been studies showing that schizophrenia or catatonia may manifest [9].

Disulfiram induced psychosis

Disulfiram induced psychosis is a rare entity; although we lack detailed and reliable data, the incidence of this disease varies in different studies. In a 1970 study, 40 000 people were treated for alcohol abuse, 5 of whom manifested with disulfiram induced psychosis [10]. According to the study, published in The American Journal of Psychiatry in 2006, 2-20% of patients who were treated with 1-2 grams of disulfiram per day developed disulfiram induced psychosis [11]. In two studies, Indian psychiatrists reported psychosis in 5 out of 53 and 6 out of 52 patients on disulfiram [12].

The mechanism of psychosis involves two toxic metabolites of disulfiram: diethyldithiocarbamate (DDC) and its metabolite carbon disulfide. DDC reduces the activity of dopamine beta-hydroxylase (DBH), an enzyme that catalyzes the metabolism of dopamine to norepinephrine. Thus, the concentration of dopamine increases in the mesolimbic system. It has also been noted, that disulfiram induced psychosis is more likely to occur when there is a positive family history of psychosis or when taking a dose higher than therapeutic doses [13].

In 2017, a comprehensive review of the published literature was conducted that included 17 cases which reported psychosis after initiation of disulfiram. The majority of the patients were men (70%). The mean age of the patients was 32.5 years (range 24-48 years). The patients were diagnosed with alcohol dependence lasting from 1 to 20 years. The duration of pharmacological treatment with disulfiram in these cases ranged from 3 days to 8 months, but most people were treated for 14-30 days before developing psychotic symptoms. Doses were up to 500 mg per day. Psychosis lasted from 1 to 14 days, the average duration was 7.5 days [14].

In most cases, the psychosis manifests while still using disulfiram, but there are some cases where the psychosis starts some time after disulfiram withdrawal. In one case, a 47-year-old man in the Netherlands developed psychosis two weeks after discontinuation of disulfiram. It was later discovered that he had a positive family history of schizophrenia and may have been more vulnerable for psychosis due to disulfiram use [15].

CONSLUSIONS

Disulfiram is an alcohol-aversive agent for the treatment of alcohol dependence; when used together with alcohol, disulfiram causes an acute toxic physical reaction of the entire body. The patient in our clinical case developed a rare psychiatric side effect of disulfiram – disulfiram induced psychosis. The patient has a family history of alcohol dependance and has been addicted to alcohol for about 15 years. The patient was administered a dose of 500 mg/day disulfiram. After about two weeks, he started experiencing side effects. Although the treatment was stopped after 37 days, disulfiram induced psychosis occurred. Predisposing factors may include psychiatric family history, personality features, early beginning of alcohol dependence, and a short period of sobriety before starting disulfiram (only 3-4 days). The psychosis manifested as an asthenic syndrome with senestopathic symptoms. Later, the patient developed a pre-delirium state (fear, insomnia, illusions, hallucinations, partial disorientation) followed by delirium. The psychosis lasted for 12 days, the treatment was successful, and the patient fully recovered. This clinical case proves that disulfiram should be administered carefully, the patient should be monitored, and we recommend abstinence from alcohol for at least 10 days before starting disulfiram.

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D. R. Survilaitė, R. Žemaitytė

DISULFIRAMINĖS PSICHOZĖS ATVEJIS

Santrauka

Įvadas. Disulfiramas – tai vienas iš trijų vaistų, kuriuos JAV Maisto ir vaistų administracija patvirtino priklausomybei nuo alkoholio gydyti. Pacientai susilaiko nuo alkoholio, kad išvengtų nemalonių alkoholio toksiškumo reiškinių. Gali pasitaikyti nepageidaujamų vaisto poveikių, dažnesni – mieguistumas, neįprastas nuovargis, galvos skausmas, metalo skonis burnoje, odos bėrimai, sumažėjęs libido. Disulfiraminė psichozė yra itin retas psichiatrinis nepageidaujamas disulfiramo poveikis.

Atvejo aprašymas. Pristatome klinikinį atvejį apie 33 metų pacientą, kuriam apie 15 metų nustatytas asmenybės sutrikimas ir priklausomybė nuo alkoholio. Pacientui buvo paskirtas disulfiramas po 4 susilaikymo nuo alkoholio dienų. Po 14 dienų disulfiramo vartojimo jis pradėjo jausti nepageidaujamus poveikius, palaipsniui ėmė trikti psichika. Pacientas buvo hospitalizuotas į Respublikinę Vilniaus psichiatrijos ligoninę, kur jam diagnozuota disulfiraminė psichozė.

Aptarimas. Disulfiramo poveikis alkoholio metabolizmui žinomas jau nuo 1940 m. Disulfiramas turėtų būti skiriamas tik motyvuotiems ir informuotiems apie alkoholio – disulfiramo reakciją pacientams. Vaistas turėtų būti skiriamas praėjus ne mažiau nei 10 dienų, nutraukus vartoti alkoholį, rekomenduojama dozė – 500 mg per dieną. Disulfiramą reikia skirti atsargiai žmonėms, sergantiems širdies ligomis, cukriniu diabetu, hipotiroidizmu, esant smegenų pažeidimui, nefritui, kepenų cirozei, epilepsijai. Taip pat disulfiramas gali veikti benzodiazepinų, kai kurių antibiotikų, antikoaguliantų, triciklių antidepresantų metabolizmą. Disulfiramas gali sukelti šalutinius poveikius, iš jų sunkesni, bet reti – regėjimo pokyčiai, sustingimas, skausmas ar silpnumas galūnėse, periferinės neuropatijos, traukuliai. Galimi psichiatriniai nepageidaujami poveikiai: nuotaikų kaita, psichozinės reakcijos, atminties sutrikimas. Trūksta patikimų duomenų apie šių nepageidaujamų poveikių paplitimą, tačiau jie pasitaiko retai. Pacientai, vartojantys disulfiramą, turi būti atidžiai prižiūrimi gydytojo.

Raktažodžiai: priklausomybė nuo alkoholio, priklausomybės gydymas, disulfiramas, šalutiniai reiškiniai, disulfiraminė psichozė.

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