Case Report

Intracerebral Bleeding Due to Disulfiram-Ethanol Reaction

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Abstract

Disulfiram is an aldehyde dehydrogenase inhibitor that causes unpleasant reaction on interaction with ethanol. Disulfiram – Ethanol Reaction (DER) results from the accumulation of acetaldehyde and presents with clinical features such as flushing, sweating, nausea, vomiting, throbbing headache, chest pain, confusion, syncope and in severe cases may lead to unresponsiveness and death. In this case, a chronic alcoholic who was on deaddiction medication from a local ayurvedic center consumed ethanol on the thirteenth day of therapy and presented with vomiting, seizures and unresponsiveness. CT brain revealed intracerebral bleeding, he underwent decompressive craniectomy and expired within two days. Chemical examination of the sample of deaddiction medication revealed the presence of disulfiram.

Keywords: Disulfiram-Ethanol Reaction, Intracerebral Bleeding

Introduction

Tetraethylthiuramdisulfide or disulfiram is a carbamoyl derivative and proteasome inhibitor known to cause adverse effects in the biological system on interaction with ethanol and thus is used as an alcohol deterrent. In as early as the 1940s, it was observed that the Danish physicians Hald and Jacobsen fell ill on consuming ethanol while under treatment for helminthic infestation with disulfiram. The Food and Drug Administration (FDA) approved disulfiram in the treatment of alcohol dependence in 1951[1]. Under the influence of acetaldehyde (a metabolite of ethyl alcohol), sympathetic nerve terminals release catecholamines which lead to vasoconstriction and the spasm of cerebral vessels results in cerebral infarction[1]

Disulfiram – Ethanol

Reaction (DER) should be differentiated from disulfiram – like reactions caused by consumption of ethanol whist on treatment with drugs such as metronidazole, sulfamethoxazole and trimethoprim, cephalosporins and the like[2]. Thus, a prompt diagnosis relies mainly on history and clinical presentation.

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Received on 09.08.2019	Accepted on 08.10.2019

Case Report

A 55-year-old chronic alcoholic male was admitted at an ayurvedic center for alcohol deaddiction therapy. On the thirteenth day of therapy, he consumed ethanol following which he developed abnormal posturing, frothing from mouth, multiple episodes of vomiting and finally lead to unresponsiveness. CT brain showed left temporoparietal intra-cranial space occupying lesion with bleeding and subarachnoid haemorrhage in the left cerebral sulcus. Emergency craniectomy and decompression was done. However, he succumbed to his illness 2 days later.

On autopsy, a craniectomy wound was noted underneath which brain matter was softened, oedematous and seen bulging out through the surgical bony deficit. On further dissection, a hematoma of size 10 x 6 x 3cm with

pulverized brain matter and granulation tissue along the margins was seen in the left cerebral hemisphere involving the temporal and parietal lobes and communicating with the superolateral surface of the left parietal lobe through a defect 2 x 1 cm. Cerebrospinal fluid was blood stained and subarachnoid haemorrhage was noted all over the brain.

Chemical examination of blood and viscera couldn't reveal any poison/drug which could be due to metabolism and elimination of the substance. However, a sample of the deaddiction medication given to the deceased at the local ayurvedic deaddiction center revealed the presence of disulfiram. The cause of death was opined as: The deceased died due to intracerebral bleeding. The interaction between the consumed alcohol and the deaddiction medication could have precipitated the bleeding.

Discussion

Ethanol is metabolized in the liver by the enzyme alcohol dehydrogenase into acetaldehyde. This acetaldehyde is further oxidized to acetate by the action of the enzyme aldehyde dehydrogenase. The acetate is released into the blood from the liver and is metabolized peripherally. Disulfiram irreversibly inhibits the enzyme aldehyde dehydrogenase resulting in the accumulation of acetaldehyde. It is this excess acetaldehyde that produces the unpleasant reaction and clinical effects[3].

Disulfiram – ethanol reaction results in an unpleasant reaction including flushing, nausea, throbbing headache, vomiting, diaphoresis, hyperventilation, palpitations, syncope, confusion, and chest pain and in severe cases causes arrhythmias, myocardial infarction, seizures, unconsciousness and death. Symptoms begin within 15 to 30 minutes of ingestion of alcohol while on disulfiram therapy, peak at 30 minutes to 1 hour and subside in the next few hours[3]. However, cases have been reported where the effects have lasted up to 2 weeks after ingestion.

Cases of disulfiram induced parkinsonism, catatonia and basal ganglia lesions due to carbon disulfide (a metabolite of disulfiram) have also been reported [4,5]. Acetaldehyde accumulation also causes histamine – mediated vasodilation and diethyldithiocarbamate (a metabolite of disulfiram) inhibits dopaminbetahydroxylase leading to noradrenaline depletion, resulting in circulatory disturbances[6, 7].

The severity of the reaction may vary from individual to individual and is usually proportional to the amount of alcohol and dose of disulfiram ingested [8]. Acetaldehyde reacts with the nucleic acid bases in DNA, damaging the mitochondria and structural proteins in various tissues such as myocardial tissue, resulting in acute and chronic myocardial damage[8]. This may present only at a subclinical level and is not detected by routine non-invasive screening techniques such as electrocardiography[9]. Nerve biopsy and electrophysiological studies after disulfiram therapy show features of axonal degenerative change[10,11].

Mild to moderate disulfiram ethanol reactions which are reversible are frequently encountered in clinical practice [12]

There is no antidote for disulfiram – ethanol reaction and treatment includes only symptomatic management with intravenous fluids, antiemetics and antihistamines. Fomepizole may be administered which inhibits the enzyme alcohol dehydrogenase and limits the production of acetaldehyde. However, the extent to which fomepizole can be used in the management of disulfiram – ethanol reactions is still being debated.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association on May 18th, 2013 includes alcohol abuse and alcohol dependence under a single disorder – AlcoholUse Disorder (AUD) with the sub-classifications as mild, moderate and severe based on the number of criteria fulfilled. According to data collected in 2014 from the World Health Organization (WHO) global survey on Resources for Prevention and Treatment of Substance Use Disorders (ATLAS-SU survey), pharmacological

treatment for alcohol use disorder is effective in only 50% cases. The treatment of substance misuse disorders such as alcohol use disorder, involves a multi-disciplinary approach with the use of antabuse drugs (disulfiram), counselling and psychotherapy, alcohol anonymous, group therapy and sometimes family therapy[13].

Conclusion

The treatment of alcohol use disorder involves a multi-disciplinary approach with the use of antabuse drugs (disulfiram), counselling and psychotherapy, alcohol anonymous, group therapy and sometimes family therapy. It should be noted that disulfiram is not a cure for alcoholism, but only used as an alcohol deterrent. No patient should be given disulfiram without his knowledge and disulfiram therapy requires close monitoring at a center where the adverse effects and emergencies due to the drug can be managed effectively. Complete physical and biochemical investigations should be done before initiating therapy and repeated at regular intervals. The patient should be educated on the adverse effects of disulfiram and disulfiram – ethanol reaction.The Honorable Apex Court in Poonam Verma vs A. Patel and others case (1996) prosecuted two homoeopathic doctors for administering allopathic drugs under Section 15(3) of the Indian Medical Council Act, 1956. Hence, public and law enforcement authorities should be vigilant about the administration of disulfiram in local ayurvedic deaddiction centers such as in this case and such practices should be terminated.

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