



Disulfiram Ethanol Reaction with Ischemic Stroke

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ABSTRACT

Disulfiram (tetraethylthiuram disulfide) has been used since decades in the treatment of alcohol addiction. It causes aversive behaviour towards alcohol due to Disulfiram Ethanol Reaction (DER). The classical DER includes flushing, sweating, tremors, nausea, vomiting, tachycardia, hypotension and restlessness. Complete recovery is the usual outcome in clinical settings. Life threatening reactions are rare but sometimes occur. Rare complications include shock, myocardial ischemia, hypertension, bronchospasm and methemoglobinemia. We present here a very rare case of ischemic stroke in a hemodynamically stable patient, which developed secondary to disulfiram-ethanol reaction. To the best of our knowledge, this is the first such reported case in literature.

Key words: Disulfiram, ethanol reaction, ischemic stroke

İskemik İnme ile Disulfiram Etanol Reaksiyonu

ÖZET

Disulfiram (tetraethylthiuram disulfide) on yıllardır alkol bağımlılığı tedavisinde kullanılmaktadır. Disulfiram Etanol Reaksiyonu (DER) nedeniyle alkole karşı caydırıcı davranışa neden olur. Klasik DER kızarma, terleme, tremor, bulantı, kusma, taşikardi, hipotansiyon ve huzursuzluk bulgularını içerir. Klinik merkezlerde tam iyileşme olağan sonuçtur. Hayatı tehdit edici reaksiyonlar nadirdir ancak bazen oluşabilir. Nadir reaksiyonlar; şok, miyokardiyal iskemi, hipertansiyon, bronkospazm ve methemoglobinemidir. Bu makalede DER'e sekonder olarak gelişen, hemodinamik olarak stabil bir hastada ortaya çıkan nadir bir iskemik inme vakasını sunduk. Bildiğimiz kadarıyla bu vaka literatürde bildirilen ilk vakadır.

Anahtar kelimeler: Disulfiram, etanol reaksiyonu, iskemik inme

INTRODUCTION

Disulfiram was first used for the treatment of alcohol dependency in 1940. The effectiveness of disulfiram in discouraging alcohol consumption is aversive in nature as it is dependent on the patient's fear of developing a disulfiram - ethanol reaction and does not produce central nervous system effects that alter an alcoholic's drinking behaviour (1).

CASE

A 35 year old man who was a chronic alcoholic and smoker was on treatment with T.Disulfiram 250mg once daily for about 3 months. He was not a known diabetic or

hypertensive. On the occasion of a festival, the patient drank about 150 ml of whisky. 10 to 15 minutes after the alcoholic drink, patient became unwell with sweating, giddiness, disturbed vision and tremors of extremities. Later he developed drowsiness and lost consciousness. There was paucity of movements of the left half of the body. He was admitted to our hospital for further evaluation and management. On admission, patient was afebrile and comatose. His blood pressure was 110/80 mmHg, pulse 80 beats per min, regular. Neurological examination revealed presence of left sided hemiplegia. Pupils were equal on both sides with preserved pupillary reaction, papilledema was present. There were no signs of meningeal irritation. Cardiovascular, respiratory and per abdomen examination were within normal limits. On

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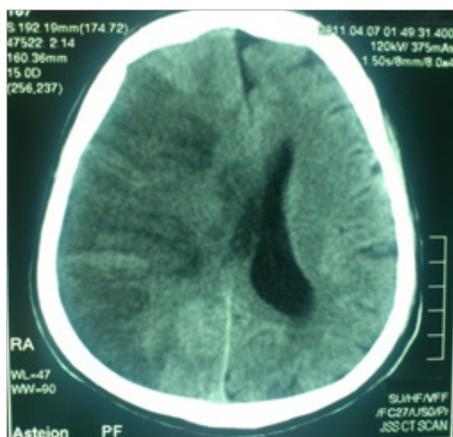


Figure 1. CT scan of head showed a large, hypodense lesion involving the right parietal, temporal, frontal and parieto-occipital lobes with mass effect suggestive of acute infarction in the right middle cerebral artery territory and adjacent watershed zones.

investigations, complete hemogram, biochemical parameters like blood sugar, blood urea, serum creatinine, liver function tests, lipid profile, serum calcium, magnesium, electrolytes and ABG were within normal limits. ECG and ECHO were normal. CT scan of head showed a large, hypodense lesion involving the right parietal, temporal, frontal and parieto-occipital lobes with mass effect suggestive of acute infarction in the right middle cerebral artery territory and adjacent watershed zones (Figure 1). Doppler study of both carotid arteries was

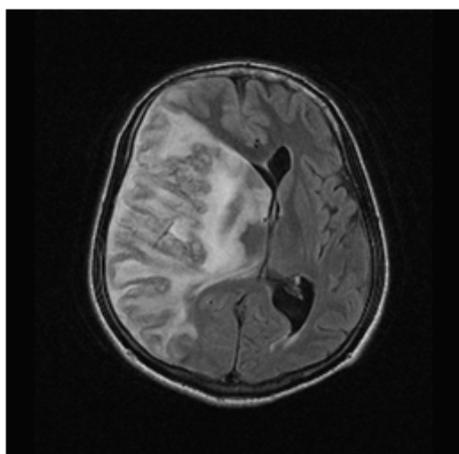


Figure 2. MR Cerebral angiogram done at one week of stroke showing haemorrhagic conversion of the infarct with increased intracerebral edema with midline shift.

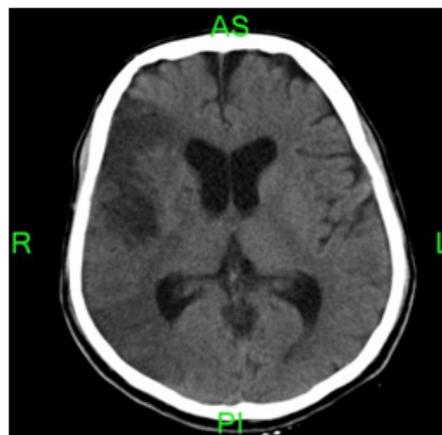


Figure 3. CT scan of head done at one month of follow up showing resolving features of old infarction in right middle cerebral artery territory and adjacent watershed zones.

normal. HIV and VDRL tests were both negative. ANA, IgM antiphospholipid antibody, lupus anticoagulant, protein C, protein S, antithrombin III, serum homocysteine levels were within normal limits. A final diagnosis of chronic alcoholism with disulfiram - ethanol reaction with ischemic stroke was made. Patient was treated with mannitol, glycerol, antiplatelet drugs, statins, folic acid and vitamin B complex supplements. Patient recovered consciousness one week after admission. MR Cerebral angiogram done at one week of stroke showed normal cerebral vessels. There was haemorrhagic conversion of the infarct with increased intracerebral edema with midline shift (Figure 2). At one month of follow up, patient's orientation was normal and the power of the affected limbs had improved to 4/5. CT scan of head done at one month of follow up showed resolving features of old infarction in right middle cerebral artery territory and adjacent watershed zones (Figure 3).

DISCUSSION

Therapeutic doses of disulfiram used as a part of a comprehensive treatment program typically range from 125-500 mg/day. Disulfiram and its metabolites impair both cytosolic aldehyde dehydrogenase-1 (ALDH1) and mitochondrial aldehyde dehydrogenase-2 (ALDH2). The inhibition by disulfiram of ALDH2 leads to a rise of acetaldehyde levels 5 to 10 times above baseline levels and a few days of treatment with disulfiram can reduce

baseline aldehyde dehydrogenase activity by 50%

Most patients taking disulfiram who are exposed to ethanol develop symptoms of DER within 15 minutes (2). The symptoms gradually peak within 30 minutes to 1 hour and then gradually subside over the next few hours. DER is due to increased serum acetaldehyde concentration generated by the metabolism of ethanol since disulfiram is a powerful inhibitor of the enzyme acetaldehyde dehydrogenase that degrades it. The accumulation of acetaldehyde that is normally metabolized rapidly by acetaldehyde dehydrogenase is responsible for many of the symptoms produced by DER (3). Signs and symptoms of DER include flushing, sweating, conjunctival injection, pruritus, light headedness, vertigo, headache, nausea, vomiting, palpitations, breathlessness, tachycardia and hypotension. Rare complications include shock, myocardial infarction, hypertension, bronchospasm and methemoglobinemia (4-6). Esophageal rupture and intracranial haemorrhage secondary to profound vomiting may occur (7,8). Symptomatic and supportive care is the mainstay of treatment.

Ischemic stroke following DER has been reported in just one case in the literature which was attributed to severe hypotension that developed following DER (9). In the present case, patient was normotensive during the development of ischemic stroke. The cerebral infarction can be attributed to the spasm of the cerebral vessel. It is well known that acetaldehyde releases catecholamines from the sympathetic nerve terminals of the blood vessels and result in vasoconstriction (10). Acute myocardial infarction (AMI) associated with DER in a young man with normal coronary arteries has been reported in the literature (11). The incidence of AMI in patients with normal or near normal coronary arteries ranges from 1% to 12% and mainly affects young people and is distinctly rare in patients older than 50 years (12). The mechanism leading to AMI in these patients remain unknown. It has been hypothesized that the probable mechanism may be temporary occlusion of the infarct related vessel by spasm or thrombus or a combination of both. In the present case, patient showed improvement in one week of treatment in the form of recovery of consciousness and at one month of follow up showed improvement in the power of the affected limbs (13-15).

To conclude, there is significant inter individual and intra individual variation in the intensity and duration of a disulfiram ethanol reaction. Though complete recovery

is the usual outcome in clinical settings, life threatening complications can occur. Disulfiram is helpful in creating aversion to alcohol but it should be used in patients who comply with the strongly advised restriction to alcohol consumption when on disulfiram therapy.

REFERENCES

1. Benitz WE, Tatro DS: *Disulfiram intoxication in a child. J Pediatr* 1984;105:487-9.
2. Goldfrank's *Toxicological Emergencies 8th edition*, McGraw-Hill Companies, New York, 2006,
3. Asmussen E, Hald J, Larsen V: *The Pharmacological action of acetaldehyde on the human organism. Acta Pharmacol Toxicol* 1948;4:311-20.
4. Ho MP, Yo CH, Liu CM, et al. *Refractive hypotension in a patient with disulfiram-ethanol reaction. Am J Med Sci* 2007;333(1):53-5.
5. Fourrier A, Mouton YJ, Raviart B, et al. *A paradoxical disulfiram-alcohol reaction: paroxysmal hypertension with convulsions and acute pulmonary edema. Lille Med* 1973;18:146-9.
6. Wilson H. *Side effects of disulfiram. Br Med J* 1962;2:1610.
7. Heath MJ, Pachar JV, Perez Martinez AL, et al. *An exceptional case of lethal disulfiram-alcohol reaction. Forensic Sci Int* 1992;56(1):45-50.
8. Guarnaschelli JJ, Zapanta E, Pitts FD. *Intracranial hemorrhage associated with disulfiram alcohol reaction. Bull Los Angeles Neurol Soc* 1972;37:19-23.
9. Prancheva MG, Krasteva SA, Tufkova SG, Karaivanova TP, Nizamova VV, Iliev YT. *Severe hypotension and ischemic stroke after disulfiram ethanol reaction. Folia Med (Plovdiv)* 2010;52(3):70-3.
10. S.Chiba, M.Tsukada. *Possible mechanism of acetaldehyde-induced noradrenaline release from sympathetic nerve terminals in isolated blood vessels. Br J Pharmacol* 1988;95:177-82.
11. Yelda Tayyareci, Esra Acaarel: *Acute myocardial infarction associated with disulfiram-alcohol interaction in young man with normal coronary arteries. Arch Turk Soc Cardiol* 2009;37(1):48-50.
12. Rigatelli G, Rossi P, Docali G. *Normal angiogram in acute coronary syndromes: the underestimated role of alternative substrates of myocardial ischemia. Int J Cardiovasc Imaging* 2004;20:471-5.
13. Lindsay J Jr, Pichard AD. *Acute myocardial infarction with normal coronary arteries. Am J Cardiol* 1984;54:902-4
14. *Adverse effects of Disulfiram and patient compliance. TN Srinivasan, TR Suresh, Jayaram Vasantha. Indian J Psychiatry* 1996;38:47-50.
15. *Status of disulfiram in present day alcoholic deaddiction therapy. Princy Louis Palatty, Elroy Saldanha. Indian J Psychiatry*;2011;53;25-9.