Severe hypotension and ischemic stroke after disulfiram-ethanol reaction

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ABSTRACT
Disulfiram (tetraethylthiuram disulfide) has been used for almost 60 years in the treatment of alcohol addiction. It causes aversive behavior due to disulfiram-ethanol reaction (DER). The classical DER includes flush, sweating, tremor, nausea, vomiting, tachycardia, moderate decrease in blood pressure and restlessness. Complete recovery is the usual outcome in clinical settings. Life-threatening reactions are rare but sometimes occur. We present a case of a 53-year-old man developing severe hypotension and ischemic stroke as a result of disulfiram treatment and ethanol intake. Use of adrenalin as a drug of choice in this critical condition, together with other therapeutic approaches led to stabilization of hemodynamics and reversal of neurological symptoms. Our case had a favorable outcome, but it should be remembered that patients unable to comply to the strong restrictions in treatment for alcohol rejection are not eligible for this therapeutic modality used in the management of alcohol dependency.

Key words: disulfiram, disulfiram-ethanol reaction, ischemic cerebral infarction

INTRODUCTION
Disulfiram (tetraethylthiuram disulfide) has been used for almost 60 years in the treatment of alcohol addiction. It induces aversive behavior in patients caused by the well known clinical phenomenon of disulfiram-ethanol reaction. The unpleasant reaction occurs after ethanol intake during disulfiram treatment.

The classical DER includes flush, sweating, tremor, nausea, vomiting, increased heart rate, moderate decrease in blood pressure and restlessness. Complete recovery is the usual outcome in clinical settings. Rare cases of life-threatening reactions like hypotension, myocardial infarction, brain hemorrhage, convulsions, unconsciousness and even death have been reported. We present a case of a 53-year-old man in whom DER manifested with severe hypotension, accompanied by ischemic stroke.

CASE REPORT
We present a case of a 53-year-old man, K. Ch., with chronic alcoholism, on treatment with disulfiram (Esperal) 250 mg daily for a week, prescribed by physician. Beginning on day 8, the dose of the drug was doubled to 500 mg daily. On day 9, 2-3 hours after intake of the prescribed dose, the patient drank approximately 300 mL of wine. About 15 min later he felt unwell, began sweating and experienced tremor of the extremities. Speech was impeded. He got confused, vomited and lost consciousness for a while. Blood pressure was 35/20.

The emergency physician applied effortil 10 mg i.m., without significant effect. A little later he added adrenalin 1 mg. i.m. and after blood pressure rose to 100/40 the patient was sent to Toxicology Dept. By the time of transportation the blood pressure had already been 130/80. There was no history of previous cerebrovascular events.

On physical examination 4 hours after onset of event the patient was alert, but confused, with extremities tremor, ataxia, dysarthria and upper lip edema. Lung auscultation showed vesicular breathing with no pathological sounds. Heart rate was regular (86/min), the blood pressure was 135/85. The patient’s abdomen was soft painless on palpation. Neurological status: central paresis of VII and XII cranial nerves on the right side with partial sensomotor aphasia. Pupils were equal in size.
with preserved pupillary reactions. No symptoms of meningeal irritation were found. Normal muscle tone and strength were present. Tendon and peristomal reflexes were bilaterally equal, but reflex zones were widened. There were no pathological reflexes. Investigation of sensory function was unsatisfactory because of the aphasia.

Paraclinical studies showed the following results: blood-gas analysis – arterial normoxia with partially compensated respiratory alkalosis; electrocardiography – sinus rhythm without repolarisation alterations; and toxico-chemical analysis – serum ethanol level – 0.35 g/L. Other laboratory (hematological and biochemical) parameters were within normal physiological ranges.

Infusion of water-electrolyte and glucose solutions was continued and therapy with nootropic (Nootropil), anticoagulant (Clexane) and antiedematous (Mannitol) drugs was initiated because of the preceding severe hypotension. The hemodynamics remained stable and no further treatment with vasopressors was necessary.

Two imaging studies of cerebrum and cerebellum were performed. Computed tomography on day 3 (native) and day 10 (i.v. contrast-enhanced) showed ischemic lesion in the left occipital area of the brain. On day 18 the brain MRI was normal (see Figs 1, 2, 3). The patient was discharged from the hospital on day 6 with recommendation to continue treatment with nootropic, vasodilating and anticoagulant drugs. At the control examination 3 months later, the patient presented with no residual neurological deficit.

**DISCUSSION**

Disulfiram was used in the treatment of alcohol dependency (AD) in 1940. It does not directly influence any AD-related biological processes but acts indirectly by creating aversive behaviour in patients which deters them from alcohol abuse due to the well-known clinical phenomenon of disulfiram-ethanol reaction. The unpleasant reaction as a result of simultaneous intake of disulfiram and ethanol is characterised with attacks of flush, sweating, weakness, tremor, confusion, nausea, vomiting, tachycardia, mild arterial hypotension.

DER is due to increased serum acetaldehyde concentrations generated by the metabolism of ethanol since disulfiram is a powerful inhibitor of the enzyme acetaldehyde dehydrogenase that degrades it. In the reported case the reaction is exceptionally severe. Development of cardiovascular collapse
has been described previously\textsuperscript{3,7} but in our case an ischemic stroke develops concomitantly which is not reported in the available literature. The circulatory disturbances in DER are mainly caused by histamine-mediated vasodilation following the acetaldehyde accumulation. Additionally, another of disulfiram metabolites – diethyldithiocarbamate suppresses the adrenergic response by inhibition of dopaminbetalhydroxylase leading to noradrenalin depletion. This is the reason why noradrenalin or adrenalin are the vasopressors of choice in such cases. Adrenalin application in our patient is one of the explanations for the fast hemodynamic recovery. Other factors probably are use of relatively low dosages of disulfiram (250 mg – 500 mg), as well as the low serum concentration of ethanol (0.35 g/L). Despite the interindividual variations of DER intensity, it is usually proportional to the amount of alcohol intake and the disulfiram dosage.

The severe hemodynamic incident in our case, though relatively short, leads to local hypoperfusion and ischemia in the basin of medial cerebral artery in the left brain hemisphere. The fast stabilization of hemodynamics and the following therapeutic interventions improve the cerebral circulation, which can probably account for the rapid reversal (approximately one week) of neurological symptoms. Some authors define such states as prolonged reversible ischemic neurological deficit, while others term it cerebral infarction with complete clinical recovery.\textsuperscript{8,9}

CONCLUSIONS

In conclusion it is worth a note that DER remains of greatest significance for demonstration of disulfiram effectiveness and for creation of aversive behavior.
in patients with alcohol dependency under clinical conditions. This case demonstrates the advantages of adrenalin application as a drug of choice in severe hypotension in DER. Despite the favorable outcome in the present case, it should be born in mind that disulfiram is not a life-saving approach to AD and patients not complying to the strong restrictions in this therapy should not be eligible for that kind of alcohol dependency management.

REFERENCE

ТЯЖЕЛАЯ ГИПОКСИЯ И ИШЕМИЧЕСКИЙ ИНФАРКТ МОЗГА ПРИ DISULFIRAM-ETHANOL РЕАКЦИИ
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РЕЗЮМЕ
Disulfiram применяется при лечении алкогольной зависимости в течение более 50 лет. Он создает аверзивное поведение посредством т. н. disulfiram-ethanol reaction /DER/. Классическая DER проявляется покраснением, потением, тремором, тошнотой, рвотой, тахикардией, умеренным понижением кровяного давления, беспокойством.

В клинических условиях, хотя и редко, наступают жизнеугрожающие состояния. Авторы сообщают о случае 53-летнего мужчины, у которого во время лечения Disulfiram-ом и приема этанола развивался тяжелая гипотензия и ишемический инфаркт мозга. Применение Adrenalin-а как средство выбора при этом критическом состоянии, как и применение других терапевтических мер, приводит к стабилизации гемодинамики и к обратному развитию неврологической симптоматики.

Несмотря на благоприятный исход при вышеописанном случае, необходимо помнить, что пациенты, не сумевшие соблюдать тяжелые регламенты для отказа от этанола, неподходящи для этого вида лечения алкогольной зависимости.