Cardiogenic Shock Caused by Disulfiram

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Drug intoxication with disulfiram is a rare condition that may lead to severe and potentially fatal cardiovascular manifestations such as cardiogenic shock. We report the case of a female patient with refractory shock after deliberate self-poisoning with disulfiram. Clinical, biochemical and echocardiographic assessment, as well as invasive monitoring confirmed cardiogenic shock associated with this drug. The known mechanisms of action of disulfiram are discussed, and the major collateral effects, especially cardiovascular effects, are described. We underscore the importance of suspecting this diagnosis and of adopting prompt and the most adequate therapeutic approach in this context.

Introduction

Deliberate self-poisoning is an important health problem worldwide, with a substantial number of patients requiring admission in Intensive Care Units (ICU) due to coma or hemodynamic instability. Antidepressants, benzodiazepines and organosphosphates are the most frequently used drugs, commonly associated with each other or with alcoholic beverages[1]. Deliberate self-poisoning with disulfiram is uncommon, but the severity of the acute complications requires that its toxic effects be recognized.

Disulfiram, which is used for the treatment of alcoholism, exerts its action when taken concomitantly with alcohol. It irreversibly inhibits the aldehyde dehydrogenase enzyme which is responsible for ethanol metabolization, thus leading to increased serum concentration of the metabolite acetaldehyde, whose toxicity results in the "acetaldehyde syndrome". The typical reaction is self-limited, with headache, flushing, dizziness, nausea, blurred vision, tremor and dyspnea[2]. When not associated with alcohol ingestion, its effects are scarce at usual daily doses. Acute intoxication at doses higher than 500 mg/day, in turn, may result in severe collateral effects, and can be lethal at doses between 10-30g/day[3].

Key Words

Shock, cardiogenic; disulfiram/poisoning, adverse effects.

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Case Report

A 49-year-old female patient with major depression and chronic alcoholism was admitted to the emergency room four hours after deliberate ingestion of 60 disulfiram tablets (15g), 16 clonazepam tablets (8mg) and six maprotiline tablets (450mg), in association with alcohol.

Her clinical examination was notable for sleeplessness, tachypnea, and poor peripheral perfusion. Blood pressure: 68 x 35mmHg; heart rate: 105 bpm. Pulmonary auscultation revealed diffuse coarse crackles.

Laboratory studies were significant for increased C-reactive protein (CRP) - 31 mg/dL. Her blood gas showed severe hypoxemia (PaO_2 66 mmHg, with FiO_2 85%).

Markers of myocardial ischemia resulted negative. Electrocardiography showed sinus tachycardia, with no changes consistent with acute ischemia. Chest radiography showed alveolar opacities bilaterally (Figure 1).

Volume resuscitation measures were introduced immediately, followed by dopamine. Blood cultures were collected and broad-spectrum antibiotic therapy was started. Despite these measures, the patient remained in refractory shock and progressed with worsening of the respiratory distress and increasing desaturation. Orotracheal intubation was required and mechanical ventilation was started. The patient was transferred to the ICU.

The clinical picture was initially interpreted as mixed - cardiogenic and septic - shock. Sepsis was assumed as the major component, having possibly originated from aspiration pneumonia due to prostration. The cardiogenic component could result from the collateral effects of the medications taken.

In order to clarify the degree of cardiac involvement, an echocardiography was performed, showing moderate impairment of the left ventricular systolic function, with a 36% ejection fraction and global hypokinesia, with no other abnormalities. In light of these findings, invasive hemodynamic monitoring with a PICCO (Pulse Induced Continuous Cardiac Output) catheter was started, confirming a profile consistent with pure cardiogenic shock, with low cardiac index and high peripheral vascular resistances (Table 1).

In this context, dopamine was replaced for dobutamine and antibiotic therapy was discontinued in the first 24 hours. A progressive decrease in CRP levels up to normal levels was later observed. Serial cardiac markers and electrocardiograms remained normal and the patient did not present rhythm or conduction disturbances.

The radiographic images were reinterpreted as cardiogenic pulmonary edema, instead of the initial hypothesis of

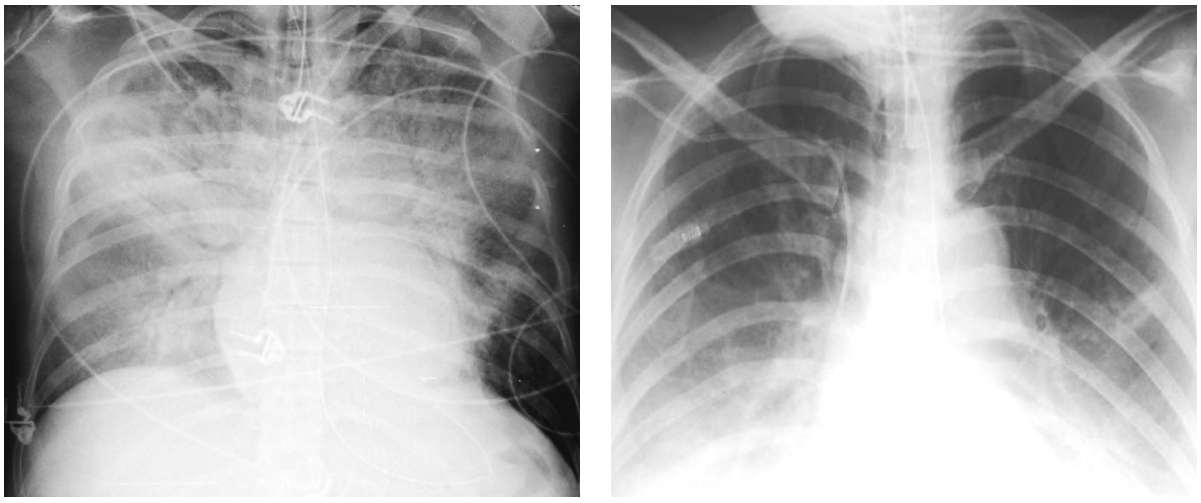

Figure. 1 - Chest radiography at ICU admission (left) showing bilateral alveolar opacities that translate into cardiogenic pulmonary edema. Radiography on day 4 (right) with resolution of the findings.

Table 1 - Invasive hemodynamic monitoring with a PICCO (Pulse Induced Continuous Cardiac Output) catheter, consistent with cardiogenic shock

	Baseline	Day 2	Day 3	Day 4
Cardiac index (N: 2.5-4 L/min)	2.33	2.06	3.2	3.2
Systolic index (N: 41-51 ml/m^2)	25.4	32	41	42
Peripheral vascular resistance index (N:1200-1800 dynsegm^2/cm^5)	2125	3916	2800	2618
Extravascular pulmonary water content index (N: 3-7 ml/kg)	13	12	10.1	9.9

pneumonia. The fact that the radiographic changes resolved within the first few hours after mechanical ventilation was started, and that the adjustment in the treatment with amines resulted in improvement of the global cardiac function corroborate this hypothesis (Figure 1).

There was resolution of the circulatory shock in 72 hours, and the ventilatory parameters improved, thus permitting extubation on day 4. Echocardiography was repeated when the patient was no longer receiving amines, and showed improvement of the systolic function (ejection fraction of 52%) and regression of the global hypokinesia. The patient had a favorable cardiovascular outcome, and at discharge from the ICU she was alert and cooperative, hemodynamically stable and had no signs of heart failure.

Discussion

After other hypotheses had been ruled out, the acute cardiogenic shock was interpreted in the context of disulfiram poisoning. With persistently normal serum cardiac marker levels and echocardiograms, the diagnosis of acute myocardial infarction was excluded. No heart valve or other structural cardiac abnormalities consistent with dilated cardiomyopathy were found.

In fact, progression to cardiogenic shock may be one of the severe complications of acute disulfiram poisoning, sometimes difficult to recognize in the initial approach to the patient. Besides being an uncommon complication, most of the patients are young and have no history of heart diseases.

The hemodynamic instability may easily be interpreted within a context of sepsis or ARDS (acute respiratory distress syndrome) instead of circulatory failure resulting from drug poisoning, and this may lead to delayed assessment of the cardiac function.

Manifestations of acute disulfiram poisoning result from the intensification of the acetaldehyde reaction when associated with alcohol, but mainly from the direct drug effects. There may be respiratory depression, neurological changes, acute myocardial infarction, arrhythmias, cardiac depression or cardiogenic shock, and even death[3,4]. When disulfiram was first introduced, very high doses used to be prescribed, sometimes of up to 3g/day, and this resulted in increased rates of severe or fatal reactions[5]. Doses were progressively adjusted, and these types of reaction are now uncommon and observed almost exclusively in cases of deliberate or accidental intake of clearly overtherapeutic doses, or in patients with previous cardiovascular disease. Nowadays, few cases are reported of cardiovascular collapse similar to that described here[6,7].

Since there is no specific antidote, aggressive support treatment has been the basis of therapy. Throughout the years, differences have been verified between the amines used as hemodynamic support, with norepinephrine proven to be more efficient than dopamine. This is thought to be due to the effects of diethyldithiocarbamate, one of

disulfiram's metabolite, which attenuates the effect of the adrenergic response to hypotension by inhibiting dopamine beta-hydroxilase, the enzyme that converts dopamine into norepinephrine[6,8]. Norepinephrine depletion at the heart and vessels permits direct action of acetaldehyde in these tissues, thus producing the typical cardiovascular symptoms, including severe hypotension. This is also possibly the mechanism that leads to the global myocardial depression which later results in shock. In view of these data, norepinephrine or epinephrine seem to be appropriate options for the treatment of such cases[9].

The efficacy of dobutamine has never been sufficiently evaluated. In the present patient, dobutamine proved to be an efficient option.

The role of the other drugs ingested in the development of the symptoms was questioned. After review of all its collateral effects, maprotiline (a tetracyclic antidepressant similar to tricyclic antidepressants) was confirmed as not being potentially able to lead to cardiogenic shock, unlike disulfiram.

The major collateral effects of tricyclic antidepressants are cardiac conduction disturbances (prolonged QRS and QT-interval or atrioventricular block). They can also lead to postural hypotension (due to alpha-1-adrenergic receptor blockade), however in a mild degree that easily reverts with fluid therapy.

Maprotiline is also less cardiotoxic than other antidepressants of the same group. Even in overdose situations, no severe hemodynamic effects such as cardiogenic shock are described, especially in patients without previous heart disease[10].

Thus, maprotiline was considered not to have contributed to the circulatory failure, and its effect, if any, would have been rapidly corrected by the aggressive therapeutic measures initially taken.

Clonazepam (benzodiazepine) has few cardiovascular effects that mainly include palpitations, and does not have either a hypotensive or depressive cardiac action[4].

Conclusion

Drug poisoning with disulfiram may have severe cardiovascular manifestations such as refractory cardiogenic shock and acute myocardial depression. These patients should be kept under strict medical surveillance and early cardiac function assessment should be performed. Invasive hemodynamic monitoring and ventilatory support in an intensive care environment may be necessary. Dopamine seems to be the least efficient amine in the management of disulfiram-induced shock.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

References

1. Novack V, Jotkowitz A, Delgado J, Novack L, Elbaz G, Shleyfer E, et al. General characteristics of hospitalized patients after deliberate self-poisoning and risk factors for intensive care admission. Eur J Intern Med. 2006; 17 (7): 485-9.
2. Wright C, Moore RD. Disulfiram treatment of alcoholism. Am J Med. 1990; 88: 647-55.
3. Petersen EN. The pharmacology and toxicology of disulfiram and its metabolites. Acta Psychiatr Scand Suppl. 1992; 369: 7-13.
4. Brunton L, Lazo J, Parker K. (eds). Goodman & Gilman: the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006.
5. Jacobsen E. Deaths of alcoholic patients treated with disulfiram. Q J Stud Alcohol. 1952; 13: 16-26.
6. Motte S, Vincent JL, Gillet JB, Deguate JP, Kahn RJ. Refractory hyperdynamic shock associated with alcohol and disulfiram. Am J Emerg Med. 1986; 4 (4): 323-5.
7. Ho MP, Yo CH, Liu CM, Chen CL, Lee C. Refractive hypotension in a patient with disulfiram-ethanol reaction. Am J Med Sci. 2007; 333 (1): 53-5.
8. Tottmar O, Hellstrom E. Blood pressure response to ethanol in relation to acetaldehyde levels and dopamine-beta-hydroxylase activity in rats pretreated with disulfiram, cyanamide and coprine. Acta Pharmacol Toxicol. 1979; 45: 272-81.
9. Moller LM, Pedersen B. High-dose adrenaline in the treatment of severe hypotensive crisis caused by disulfiram ethanol reaction. Ugeskr Laeger. 1990; 152: 2437-8.
10. Rays J, Wajngarten M. Antidepressivos e doenças cardiovasculares. Rev Soc Cardiol Estado de São Paulo. 1998; 8 (6): 11-6.