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CASE REPORT

Delayed onset of impaired consciousness complicated with ketoacidosis after disulfiram overdose

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Abstract

Background: We report a case of disulfiram overdose that caused a delayed onset of impaired consciousness and ketoacidosis.

Case presentation: A 61-year-old man was transferred to our hospital following a suicide attempt. The patient lost consciousness after an overdose of disulfiram and brotizolam. He was diagnosed with acute drug intoxication and was intubated. On day 2, he showed an improved consciousness response and was successfully extubated. On day 5, the state of consciousness worsened again, and ketoacidosis progressed. The patient required hemodialysis and suffered from impaired consciousness for the following 2 weeks. Eventually, he recovered gradually and was discharged to the rehabilitation ward.

Conclusions: The delayed appearance of symptoms after the disulfiram overdose was thought to be related to the slow metabolism of disulfiram in the body. Our case suggests the necessity of careful follow-up for delayed impaired consciousness.

KEYWORDS
disulfiram, encephalopathy, intoxication, ketoacidosis, overdose

BACKGROUND

Disulfiram is a drug used to treat alcoholism.[1] To the best of our knowledge, this is the first report of a disulfiram overdose that has led to the delayed onset of impaired consciousness and ketoacidosis that occurred simultaneously. Herein, we report the findings related to this case in conjunction with a review of existing published works.

CASE PRESENTATION

A 61-year-old man ingested 100 packets of disulfiram 0.5 g and 86 tablets of brotizolam 0.25 mg with 20 g alcohol to commit suicide. He was found unconscious and transferred to our emergency and critical care center. His medical history included depression and alcoholism, for which he was being treated at a psychiatric clinic, and a history of stent placement due to angina. Following the initial physical examination upon arrival at our facility, he was unconscious and disoriented (classified with a Glasgow Coma Scale score of 6 [E1V1M4]). His respiratory rate, pulse rate, blood pressure, and body temperature were maintained at 18 breaths/min, 60 b.p.m., 129/87 mmHg, and 36.0°C, respectively. His oxygen saturation was 100% while he was receiving 10 L/min oxygen through a face mask. His initial arterial blood gas (ABG) analysis revealed the following: pH 7.397, $PaCO_2$ 43.4 mmHg, PaO_2 304 mmHg, HCO_3^- 26.2 mmol/L, SaO_2 100%, and lactate 2.6 mmol/L. There was no abnormality in blood glucose or electrolytes, and the initial head computed tomography and electroencephalogram showed no abnormal findings. The clinical course is shown in Figure 1, and laboratory data are summarized in Table 1. He was diagnosed with acute drug intoxication based on the situation at the scene of the incident and was intubated for airway protection preceding admission to the intensive care unit. There were no gastrointestinal symptoms or facial flush that is associated with a disulfiram–ethanol reaction (DER) on admission. On day 2 of hospitalization, the patient was

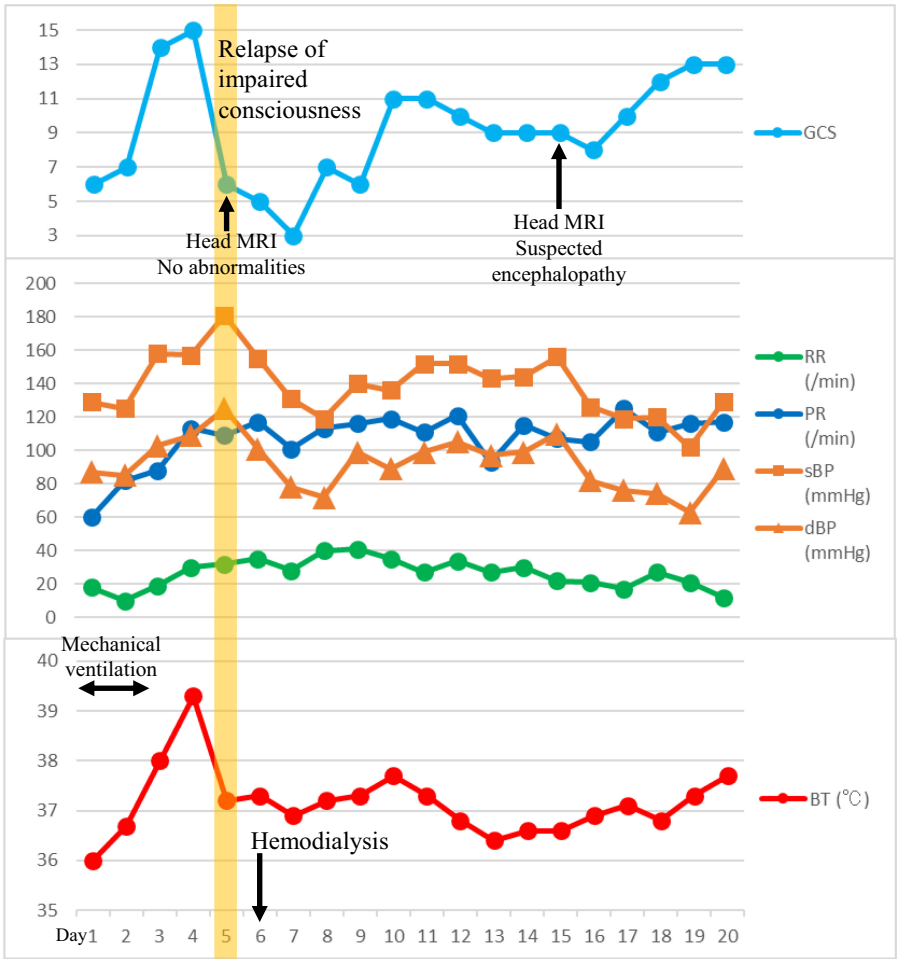

FIGURE 1 Clinical course of a 61-year-old man with overdose of disulfiram and brotizolam. BT, body temperature; dBP, diastolic blood pressure; GCS, Glasgow Coma Scale; MRI, magnetic resonance imaging; PR, pulse rate; RR, respiratory rate; sBP, systolic blood pressure.

extubated due to improved consciousness and discharged from the intensive care unit on day 4.

However, on day 5, impaired consciousness relapsed, and the level of consciousness fluctuated (Glasgow Coma Scale scores, 3–13). Notably, no other typical clinical symptoms associated with DER were observed; his ABG analysis on day 5 revealed the following: pH 7.338, $PaCO_2$ 19.5 mmHg, PaO_2 83.9 mmHg, HCO_3^- 10.5 mmol/L, SaO_2 96.0%, and lactate 1.4 mmol/L. These results indicated metabolic acidosis with elevated ketone bodies (3105 μmol/L for acetoacetic acid and 3340 μmol/L for 3-hydroxybutyric acid), and other laboratory results as shown in Table 1. Apart from these, there were no abnormalities in the head computed tomography, head magnetic resonance imaging (MRI), electroencephalogram, and cerebrospinal fluid examinations, which could explain the reappearance of the impaired consciousness. Other causes of impaired consciousness, such as vitamin deficiency, alcohol withdrawal delirium, and psychiatric reactions, were identified as differential causes, but were considered less likely because vitamins had been supplemented by injection since admission, and none of these causes could explain the appearance of ketoacidosis. As no other factors could have caused impaired consciousness and ketoacidosis reappearance, we considered that the disulfiram intoxication was associated with the above-mentioned condition. Furthermore, although there was no apparent development of acute kidney injury, metabolic acidosis was not improved with fluids and sodium bicarbonate treatment. Therefore, hemodialysis was carried out on day 6 due to the exacerbation of metabolic acidosis. The patient did not require subsequent hemodialysis after this. Head MRI on day 15 revealed a new hyperintensity from the bilateral middle cerebellar peduncle to the cerebellar white matter on transverse relaxation (T2)-weighted fluid-attenuated inversion recovery images (Figure 2), which disappeared on follow-up MRI carried out on day 45. In addition, it is worth noting that, apart from unconsciousness, no neurological symptoms such as dizziness or cerebella ataxia were observed. Therefore, although the association between the imaging finding and the clinical presentation is unclear, it could suggest that encephalopathy might have been present. Eventually, after 2 weeks of prolonged unconsciousness, the patient showed gradual improvement in the level of consciousness and was later transferred to the rehabilitation ward on day 60.

TABLE 1 Laboratory data of a 61-year-old man with overdose of disulfiram and brotizolam.

	Day 1	Day 4	Day 5	Day 6	Day 8	Day 12	Day 17
Hematology							
White blood cells (/μL)	5800	9100	10,600	10,500	8300	12,000	11,400
Red blood cells (10^4/μL)	390	348	354	363	347	308	329
Hemoglobin (g/dL)	12.3	11.1	11.3	11.5	11.1	9.7	10.6
Hematocrit (%)	36.1	32.4	32.8	33.2	32.4	28.9	31.4
Platelets (10^4/μL)	17.3	14.1	14.5	18.4	18.0	26.2	60.3
Biochemistry							
Albumin (g/dL)	3.5	3.1	3.0	2.7	2.3	2.1	2.4
Creatine kinase (U/L)	83	753	4135	9096	5465	354	42
Aspartate aminotransferase (IU/L)	40	38	136	294	341	56	176
Alanine aminotransferase (IU/L)	27	26	47	110	176	95	308
Lactate dehydrogenase (IU/L)	177	194	349	511	745	524	357
Alkaline phosphatase (IU/L)	194	171	181	–	–	313	897
γ-Glutamyl trans peptidase (IU/L)	103	94	105	102	108	138	340
Blood urea nitrogen (mg/dL)	10.7	10.2	12.9	17.4	17.2	17.4	23.3
Creatinine (mg/dL)	0.72	0.66	0.62	0.67	0.49	0.46	0.52
Sodium (mmol/L)	141	142	141	148	148	139	135
Potassium (mmol/L)	2.9	4.3	4.3	4.2	3.3	3.6	5.7
Chloride (mmol/L)	105	105	107	111	111	106	102
C-reactive protein (mg/dL)	0.04	13.07	25.94	27.81	5.64	4.40	1.41
Acetoacetic acid (μmol/L)	–	–	3105	–	883	635	51
3-Hydroxybutyric acid (μmol/L)	–	–	3340	–	905	861	42
Arterial blood gas							
pH	7.397	–	7.338	7.409	7.436	7.566	–
$PaCO_2$ (mmHg)	43.4	–	19.5	19.8	41.1	22.9	–
PaO_2 (mmHg)	304.0	–	83.9	92.8	96.9	107	–
HCO_3^- (mmol/L)	26.2	–	10.5	11.8	27.3	20.8	–
SaO_2 (%)	100.0	–	96.0	96.8	97.5	98.8	–
Lactate (mmol/L)	2.6	–	1.4	1.7	0.5	0.5	–
Blood glucose (mg/dL)	153.0	–	93.0	157.0	174.0	139.0	–

DISCUSSION AND CONCLUSIONS

Disulfiram is a therapeutic agent for alcohol dependence. Ethanol is mainly metabolized to acetaldehyde in the liver and then oxidized to acetic acid by aldehyde dehydrogenase.[1] Disulfiram is an aldehyde dehydrogenase inhibitor that causes acetaldehyde accumulation by inhibiting the metabolism of acetaldehyde to acetate.[1] High concentrations of acetaldehyde act as a powerful vasodilator and cause unpleasant DER side-effects manifested in the forms of headache, vomiting, flushing, palpitation, and dizziness.[1] In severe cases, it can result in distributive shock that resembles anaphylactic symptoms and can be fatal. Disulfiram also causes toxicity to the central and peripheral nervous systems due to its toxic metabolites, but the exact mechanism is unknown.[2] Disulfiram is metabolized to toxic metabolites, such as diethyldithiocarbamate and carbon disulfide (CS_2), thus causing acute and chronic toxicity.[1] Copper chelation with diethyldithiocarbamate is involved in the inhibition of dopamine β-hydroxylase, which converts dopamine to norepinephrine, enhances dopamine, and depletes norepinephrine levels.[3,4] The resulting excess dopamine, copper deposition in the basal ganglia, and CS_2 accumulation could be possible explanations for the development of encephalopathy.[5,6]

It is worth noting that impaired consciousness reappeared late after the disulfiram overdose. This might be related to the slow metabolism of disulfiram in the body, with approximately 20% of the drug remaining in the body for 1–2 weeks after ingestion.[1] Interestingly, in the present case, a benzodiazepine was taken simultaneously with disulfiram and was metabolized faster than disulfiram. We speculated that in the beginning, the action of the benzodiazepine led to initial impaired consciousness, followed by a delayed disulfiram action, which then caused the

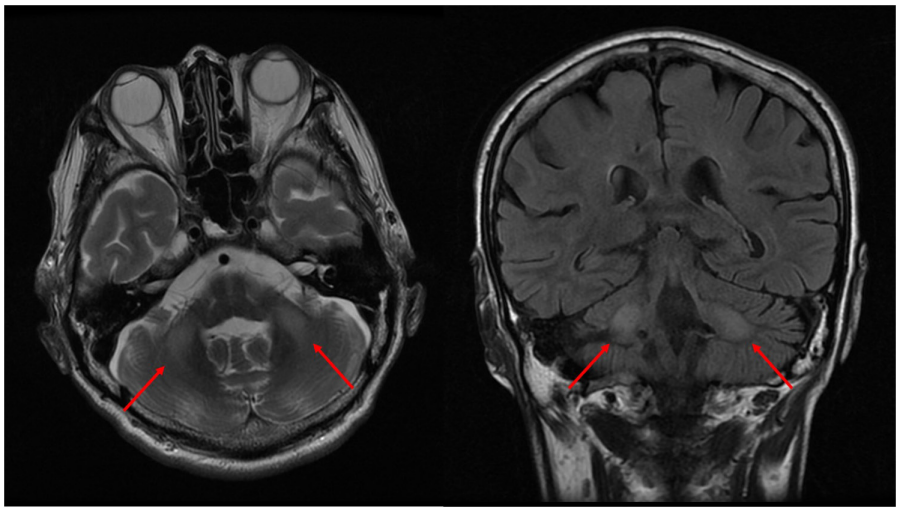

FIGURE 2 Head magnetic resonance imaging on day 15 of hospitalization of a 61-year-old man with overdose of disulfiram and brotizolam. The images reveal a hyperintensity from the bilateral middle cerebellar peduncle to the cerebellar white matter on transverse relaxation-weighted and fluid-attenuated inversion recovery images (arrows).

relapse of impaired consciousness. Although the development of encephalopathy and the slow metabolism of disulfiram could have also been associated with the delayed onset of impaired consciousness, no similar case reports were found, and further investigations are required to validate this causality.

We could not find similar case reports on ketoacidosis after an overdose of disulfiram in published works. Ethanol is oxidized to acetic acid through the formation of acetaldehyde in the liver and finally becomes acetyl-CoA, in which nicotinamide adenine dinucleotide (NAD^+ in its oxidized form and NADH in its reduced form) in hepatic mitochondria is reduced to NADH.[7] It is known that long-term alcohol intake increases the NADH/NAD^+ ratio due to the accumulation of NADH in hepatic mitochondria, thus suppressing the tricarboxylic acid (TCA) cycle.[7] When the TCA cycle is suppressed, the accumulated acetyl-CoA is metabolized to ketone bodies.[7] This metabolic response is related to the mechanism of alcoholic ketoacidosis.[7] In the present case, we considered that the accumulation of acetyl-CoA was delayed because disulfiram slowed down the metabolism of ethanol. We speculated that the accumulation of NADH in the hepatic mitochondria due to long-term ethanol intake suppressed the TCA cycle, and the slowly accumulated acetyl-CoA was metabolized to ketone bodies, leading to the delayed ketoacidosis observed. In animal models, it was reported that disulfiram increased blood acetone levels but not the other ketone body fractions, such as those of acetoacetic and 3-hydroxybutyric acids.[8] Therefore, it is presumed that disulfiram is involved in the inhibition of the acetone metabolic pathway; however, it remains unclear whether this mechanism was associated with ketoacidosis in this case.

In conclusion, we report the case of a patient with delayed onset coma symptoms complicated with metabolic acidosis after an acute disulfiram overdose. As we have described, disulfiram intoxication might have influenced the delayed onset symptoms. In addition, given that our patient developed a loss of consciousness on the day 5, we suggest that it is necessary to set a careful follow-up period of approximately a few days to a week in consideration of the risk of late symptom onset, during which the consciousness levels and ABG analysis should be closely monitored.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol with approval no. and committee name: N/A.
Informed consent: Informed consent for publication was obtained from the patient.
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.

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