

Anesthesiology
67:809-810, 1987

Disulfiram-like Reaction Associated with Carmofur after Celiac Plexus Alcohol Block

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Many drugs produce disulfiram-like reactions.¹ No reactions have been reported from administration of carmofur (1-Hexyl carbamoyl-5-fluorouracil), an anti-cancer drug. We recently observed a patient under treatment with carmofur who had a disulfiram-like reaction after a celiac plexus alcohol blockade.

CASE REPORT

A 65-yr-old, 52-kg, 160-cm man was scheduled for right celiac plexus alcohol blockade in an attempt to reduce intractable right hypochondrial pain from recurrent pancreatic carcinoma. The obstructive symptoms had been surgically treated by choledochostomy 2 months previously. The postoperative medical management consisted of carmofur chemotherapy. Every day, 500 mg of carmofur was given for 25 days prior to the alcohol blockade. No abnormalities in laboratory studies were observed except for diabetes mellitus. There were no known medical allergies and no history of alcohol use. Computed axial tomography of abdomen revealed mild enlargement of pancreas and tumor invasion toward para-aortic lymph nodes.

Under image intensifier direction, a 12-cm 22-gauge needle was placed in the prevertebral areolar tissue at the L-1 level;² 1% mepivacaine 15 ml with 60% Urographine® was injected. There were no acute complications, and the patient obtained satisfactory pain relief. Subsequently, 99.5% ethyl alcohol, 15 ml, was administered after negative aspiration test.

Ten minutes after the administration, he experienced facial flushing. Within 30 min, he complained of general flushing accompanied by hypotension (BP 60/30 mmHg), tachycardia (HR 128 bpm), and diaphoresis. Hypotension continued for 3 h in spite of massive intravenous fluid infusion and sympathomimetic treatment. These symptoms abated approximately 4-6 h after onset. Seven hours later, he recovered from this reaction completely.

Next morning, he complained of left upper localized abdominal pain. Once more blockade was requested for remission of pain. Left celiac plexus alcohol blockade performed the following day (7 days post-drug administration) produced no ill effects. He had no history of a similar untoward reaction to alcohol ingestion.

During the first blockade, venous blood, 2 ml, was taken several

TABLE 1. Blood Concentrations of Ethanol and Acetaldehyde After the Celiac Plexus Alcohol Blockade

Time After the Blockade	Ethanol (mM)	Acetaldehyde (μM)
2 h 10 min	2.76	82.05
3 h 30 min	1.34	59.30
4 h 30 min	0.29	23.89
5 h 40 min	0.03	5.23
6 h 40 min	0.03	4.39
12 h 10 min	0.02	2.17
15 h 10 min	0.03	1.65
16 h 20 min	0.04	0.18

times, and concentration of ethyl alcohol and acetaldehyde was measured (table 1).³ The clinical signs described above were typical and the response to be expected after high blood concentration of acetaldehyde. The maximum level was 82.05 μM 2 h after the blockade. Thereafter, the concentration decreased gradually. Subsequently, phenotype of aldehyde dehydrogenase (ALDH) isozyme in the hair roots was determined by isoelectric focusing according to the method of Goedde *et al.*⁴ Our patient was deficient in ALDH I isozyme.

DISCUSSION

The symptoms experienced by our subject are strikingly similar to those associated with the typical disulfiram reaction. Disulfiram-like reaction is known to occur also in the subjects taking the Cephem Class of antibiotics,^{5,6} chloramphenicol, isoniazid, tolazoline, and chlorpropamide.⁷ No reports exist of disulfiram-like reaction to carmofur in association with celiac plexus alcohol blockade. This reaction is believed to result from the accumulation of acetaldehyde. Normally, acetaldehyde does not accumulate in blood and tissues because of rapid oxidation by ALDH. In the presence of disulfiram, however, the acetaldehyde concentration rises because disulfiram competes with NAD for the active center of ALDH, thus reducing the rate of oxidation of acetaldehyde.⁸

A clinical diagnosis of disulfiram-like reaction is made by the characteristic symptoms, such as facial or whole body flushing, palpitations, hypotension, dyspnea, vomiting, dizziness, and a pounding headache. The specific diagnosis is made by determining the accumulation of acetaldehyde in the blood sample. The maximum level in our case was 82.05 μM. Previously, we confirmed that the acetaldehyde blood concentrations ranged from 13.85 μM to 17.26 μM in the subjects who were

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Received from the Department of Anesthesiology, Faculty of Medicine, Kyoto University, Kyoto, Japan; and the Department of Legal Medicine, Faculty of Medicine, Kobe University, Kobe, Japan. Accepted for publication May 19, 1987.

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Key words: Alcohol; carmofur; disulfiram. Anesthetic technique: celiac plexus; regional.

deficient in ALDH I, in 2 h following the same procedure.⁹ Compared with the previous data, our patient's acetaldehyde concentration was 7.5 times higher 2 h after the blockade; and 10 times higher 5 h after the blockade. Furthermore, clinically, the hypotension persisted for 7 h in spite of massive infusions of lactated Ringer's solution and sympathomimetic treatment. To our regret, the acetaldehyde level could not be measured because the patient's consent was not obtainable at a second blockade. However, he did not experience these symptoms at the second time. Thus, we conclude that a disulfiram-like reaction occurred in this patient taking carmofur.

Alcohol is rapidly absorbed into the blood stream following celiac plexus blockade. Our previous experiments show that the mean blood ethanol levels reached a peak value of about 5 mM in both deficient and normal groups 1 h after injection of identical amounts of ethanol.⁹ This value is lower than the level used for a legal definition of acute intoxication.¹⁰ In our case, the ethanol level was not significantly different from our previous data. Thus, carmofur seems not to influence blood alcohol concentrations. Furthermore, the symptoms experienced by our patient are not the signs of acute alcohol intoxication.

Carmofur is a derivative of 5-fluorouracil, a common anti-cancer drug. It rapidly achieves therapeutic blood concentration following oral administration. It is confirmed that half-lives are 70 min in the rapid phase and 5 h in the slow phase after administration in a pharmacokinetic study.¹¹ This drug produced minor adverse effects in 34% of the patients studied.¹² One incident of alcohol intolerance has been reported by Yoshida *et al.*¹³ Thus, it may be advisable to avoid alcohol ingestion after carmofur treatment.

As a result of studying the genetic polymorphism of ALDH, four isozymes are separated, which are named ALDH I, II, III, and IV, respectively. About one-third of all Japanese are deficient in ALDH I, which showed a low K_m value for acetaldehyde.¹⁴ We confirmed that the acetaldehyde blood levels were significantly different between deficient and normal subjects.⁹ Therefore, we compared data in our patient with the previous data in ALDH I deficient subjects.

In summary, a case of disulfiram-like reaction following celiac plexus alcohol blockade was presented. The probability of such a reaction can be judged by patient's high acetaldehyde blood concentration. To prevent this reaction, an alcohol blockade should not be performed for 7 days after treatment with carmofur.

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