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Case report

First case report of cefmetazole-induced disulfiram-like reaction

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ABSTRACT

Disulfiram-like reactions occur when alcohol is consumed concurrently with certain drugs and can sometimes be fatal. Some cephalosporins such as cefoperazone could cause disulfiram-like reaction, known as cephalosporin-induced disulfiram-like reactions (CIDLRs). We describe a case of cefmetazole (CMZ)-treated CIDLR triggered by alcohol consumption. A 72-year-old Japanese man, treated with CMZ for perforated appendicitis and subsequent paralytic ileus, presented with skin flushing and chest discomfort, developing 30 min after consuming usual meals and alcohol. CIDLR was diagnosed due to recent use of CMZ and the symptoms alleviated without any medication. This is the first case report of a CMZ-induced disulfiram-like reaction.

Introduction

Disulfiram, a drug used to treat chronic alcohol dependence, works by inhibiting aldehyde dehydrogenase (ALDH), a major hepatic enzyme of the oxidative pathway of alcohol metabolism, which converts acetaldehyde to acetate. This leads to an accumulation of acetaldehyde when alcohol is consumed. At therapeutic doses of disulfiram, the increased levels of acetaldehyde cause a variety of unpleasant symptoms such as diaphoresis, palpitations, facial flushing, nausea, vertigo, hypotension, and tachycardia. This combination of symptoms is known as the disulfiram-alcohol reaction, which serves as a deterrent to drinking [1]. Cephalosporins, particularly those containing methylthiotetrazole (MTT) substituents, such as cefoperazone, can cause reactions similar to disulfiram-like reactions, which are known as cephalosporin-induced disulfiram-like reactions (CIDLRs) [2–4]. These reactions occur because the MTT group inhibits ALDH, leading to the accumulation of acetaldehyde when alcohol is consumed. CIDLR can occur when alcohol is consumed within 72 h of taking the antibiotic. The manifestations of CIDLR vary from mild, such as facial flushing, nausea, or vomiting, to severe, such as angioedema, hypotension, shock, or even death in extreme cases [4].

Cefmetazole (CMZ), a cephamycin antibiotic with a broad spectrum of activity against *Enterobacterales*, is commonly used to treat invasive urinary tract infections and acute cholangitis in Japan [5,6]. Recently, CMZ has gained attention as an alternative to carbapenems for treating infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* [7]. This interest is due to the increasing prevalence of ESBL-producing bacteria and the need to preserve carbapenems, which are often considered last-resort antibiotics [8].

As one of its side effects, CMZ, due to the presence of the MTT side chain, is known to cause vitamin K deficiency and subsequent coagulation disorders [9]. However, CIDLR associated with CMZ use is not widely reported. Herein, we report a case of CIDLR in a patient with perforated appendicitis who was misdiagnosed and treated for anaphylaxis. To the best of our knowledge, this is the first reported case of a CMZ-induced disulfiram-like reaction.

Case report

A 72-year-old Japanese man weighing 73.5 kg, who had previously been healthy, was brought to our emergency department (ED) with perforated appendicitis leading to paralytic ileus. He was admitted to our hospital and treated conservatively with intravenous CMZ (1 g q8h) for 11 days. He was not provided any medications other than CMZ and Ringer's solution during admission. He received intravenous CMZ in the morning and was discharged in the afternoon.

After returning home, the patient had his usual meal for dinner along with 350 mL beer and 180 mL sake to celebrate his hospital discharge. He had previously consumed these kinds of foods, including alcohol, and had no known drug or food allergies. However, 30 min after dinner, which was 10 h after the last CMZ infusion, he developed skin flushing throughout his body and chest discomfort. The patient was immediately transferred back to our hospital ED. The symptoms persisted for an hour after the onset. He reported no symptoms of headache, nausea, diarrhea,

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abdominal pain, wheezing, skin itching, rashes, or facial swelling. His wife had also consumed the same dinner but had not developed any adverse symptoms.

Initial vital signs in the ED were as follows: body temperature, 36.5 ℃; heart rate, 94 beats/min; respiratory rate, 20 breaths/min; SpO_2, 92 % (on room air); Glasgow Comma Scale, 15; and blood pressure, 118/60 mmHg. Due to chest discomfort and hypoxia, the physician at the ED referred him to a cardiologist to rule out myocardial infarction (MI). However, no abnormal findings were observed on electrocardiography, cardiac ultrasonography, or cardiac biomarker testing. Physical examination revealed diffuse erythema on his trunk and extremities without wheezing, mucosal swelling, or pruritus. Anaphylaxis was suspected, and the patient immediately received intramuscular adrenaline (0.5 mg, single injection), which did not improve the patient's symptoms. Therefore, intravenous histamine H1/2 receptor antagonists (5 mg d-chlorpheniramine maleate and 20 mg famotidine, single injection) were administered. Skin flushing disappeared 10 min after infusion, but chest discomfort persisted.

After initiation of methylprednisolone sodium succinate injection (125 mg, single injection) to prevent a late-phase anaphylactic response, the patient was referred to the internal medicine department for further examination because of the suspected anaphylaxis.

The patient's medical history was significant for recent perforated appendicitis; however, he was otherwise healthy. On admission to the internal medicine department, his SpO_2 levels returned to normal (98 % on ambient air), and the diffuse erythema had completely disappeared, although his mild chest discomfort persisted. Laboratory tests showed an elevated white blood cell count (13.3×10^9/L) with 78.8 % neutrophils, 16.3 % lymphocytes, and 0.7 % eosinophils but was otherwise normal. The serum creatinine level was 0.68 mg/dL (eGFR 86.69 mL/min/1.73 m^2). The following day, the blood cell counts were within the normal range, and he no longer experienced chest discomfort. The patient was discharged without any prescription, and diffuse erythema or chest discomfort did not appear at the follow-up visit a month later. The probability of CMZ-induced CIDLR in this case is estimated using the Naranjo Algorithm, yielding a total score of 5, indicating that adverse drug reaction is probable [10]. The diagnosis of CIDLR was confirmed as alcohol poisoning-like symptoms following intravenous CMZ injection and consumption of a small amount of alcohol dissipated shortly after symptomatic treatment.

Discussion

We have described the case of a patient who developed CIDLR after CMZ administration for perforated appendicitis. Patients with CIDLR can be easily misdiagnosed as having MI or alcohol or cephalosporin allergy [4]. To avoid incorrect documentation of cephalosporin-induced severe allergic reactions and unnecessary use of non-cephalosporin second-line antibiotics for future infections, differentiating CIDLR from drug allergy is vital.

A retrospective review of 78 CIDLR cases revealed several characteristics. First, all patients developed CIDLR within 60 min of consumption of alcohol or antibiotics. Second, after receiving intravenous antibiotics, the amount of alcohol that could be tolerated was reduced by half. Last, common symptoms included chest discomfort, tachycardia, and facial flushing [4]. In the present case, the patient developed chest discomfort and skin flushing 30 min after drinking half as much alcohol as usual. To minimize unnecessary treatment, CIDLR should be considered in individuals who drink alcohol and exhibit symptoms that mimic anaphylaxis or MI. Alcohol ingestion often results in dry flushing in patients with ALDH polymorphisms, which is common among Asians [11]. In the present case, the patient experienced flushing as a disulfiram-like reaction. Considering that administration of antihistamines alleviated the flushing symptoms, the condition could potentially be misdiagnosed as anaphylaxis. Acetaldehyde has been suggested to contribute to the development of various hypersensitivity reactions by directly increasing the histamine release from mast cells [12]. In addition, pretreatment with antihistamines has been shown to decrease flushing associated with alcohol ingestion in Asian populations [13]. Antihistamines can reduce skin flushing caused by CIDLR, which should be treated independently from anaphylaxis. Although the product label of CMZ indicated disulfiram-like effects as one of the potential side effects [14], the patient was not instructed to avoid alcohol consumption for a week after hospital discharge. Alcohol can remain in the body for approximately 12 h, whereas antibiotics take several days to completely metabolize in the body [4]. Thus, patients need to be instructed not to consume alcoholic beverages within a week following cephalosporin treatment, or vice versa [4]. Notably, the amount of time for any patient to avoid alcohol while on cefmetazole is contingent to the patient's renal function and can potentially be longer than a week.

This case report has limitations, including the missing objective laboratory data to support the diagnosis such as ethanol, aldehyde, and CMZ serum concentrations, and the lack of allergy testing to rule out other differential diagnosis of anaphylactic reaction.

Conclusion

CIDLR is distinguished by acute alcoholic toxicity, such as chest discomfort, tachycardia, and facial flushing, which occurs after consuming a lower-than-average amount of alcohol with or immediately following the administration of certain antibiotics. Because of the presence of the MTT side chain, CMZ causes a disulfiram-like reaction. Clinicians and pharmacists should remain vigilant and proactive, and must inform patients of the potential risks of the combined use of alcohol and cephalosporins, including CMZ, to prevent CIDLR.

CRediT authorship contribution statement

Toshiyuki Nakanishi: Writing – original draft. **Taku Harada:** Writing – review & editing. **Mori Nakai:** Writing – review & editing. **Satoshi Kutsuna:** Writing – review & editing, Supervision.

Consent

The patient provided written informed consent for publication of this case report. A copy of the written consent is available for the journal.

Ethical approval

The patient provided written informed consent for publication of this case report. A copy of the written consent is available for the journal.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of interest

None.

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