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Case Report

Refractory status epilepticus, serious rhabdomyolysis, acute liver injury, and pancytopenia after a massive intake of ethyl methanesulfonate: a case report

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Abstract: Ethyl methanesulfonate is a mutagenic, alkylating agent and considered harmful to humans at levels greater than a certain threshold; however, the toxicity at high doses remains unclear. We report a case of a Japanese man who presented with status epilepticus, rhabdomyolysis, pancytopenia, and hair loss after accidental ingestion of a massive amount of ethyl methanesulfonate. The patient completely recovered with critical care, including multiple antiepileptic drugs, renal replacement therapy, blood transfusion, granulocyte colony-stimulating factor therapy, and antibacterial/fungal prophylaxis. The case indicates that ethyl methanesulfonate causes neurotoxicity, hepatotoxicity, hematotoxicity, and renal toxicity, which can be successfully treated with appropriate palliative therapies.

Keywords: Ethyl methanesulfonate, acute toxicity, status epilepticus, rhabdomyolysis, pancytopenia

Introduction

Ethyl methanesulfonate (EMS) is a mono-functional alkylating agent that causes genotoxic and carcinogenic effects by direct methylation of DNA; it has been used in experimental work as a model mutagen [1]. EMS is considered harmful to humans owing to its carcinogenicity, particularly the toxicity to reproductive organs and initiation of tumor-forming processes at doses of 50-100 mg/kg in mice [2]. EMS intoxication in humans was first reported with EMS contamination of Viracept® (nelfinavir mesylate; protease inhibitor) tablets as a result of a production-related incident. Patients with HIV were potentially exposed to daily doses of up to 55 μg/kg for 3 months [3]. A number of in vivo genotoxicity studies and human risk assessment studies were performed for this incident; EMS genotoxicity showed threshold-like dose responses for both chromosome damage and gene mutation in various organs in mice that were treated for up to 4 weeks, whereas ethylation of hemoglobin at the N-terminal valine linearly increased with dose. The difference between adduct formation in DNA and proteins was interpreted as saturation of the alkylguanine DNA alkyltransferase repair system above a certain threshold dose [4, 5]; thus, the cells were able to repair large amounts of DNA ethylations induced by EMS without an increase in mutation frequencies. With extrapolation to humans of data from toxicokinetic investigations in a wide variety of species, an acceptable daily exposure of 100 μg EMS has been proposed [6].

However, the effect of a large quantity of EMS in humans is not understood. Previous reports have indicated genotoxicity, as indicated by productive organ malfunction, at doses of up to 250 mg/kg EMS in various animals, but general toxicity was not described. Here, we present a case of multiple acute toxicities observed in a patient who ingested approximately 1 g/kg EMS and subsequently developed refractory status epilepticus, serious acute renal failure, liver injury, hair loss, and severe pancytopenia; he successfully recovered with palliative treatment.

Case report

A 44-year-old Japanese male scientist visited our emergency outpatient service because of

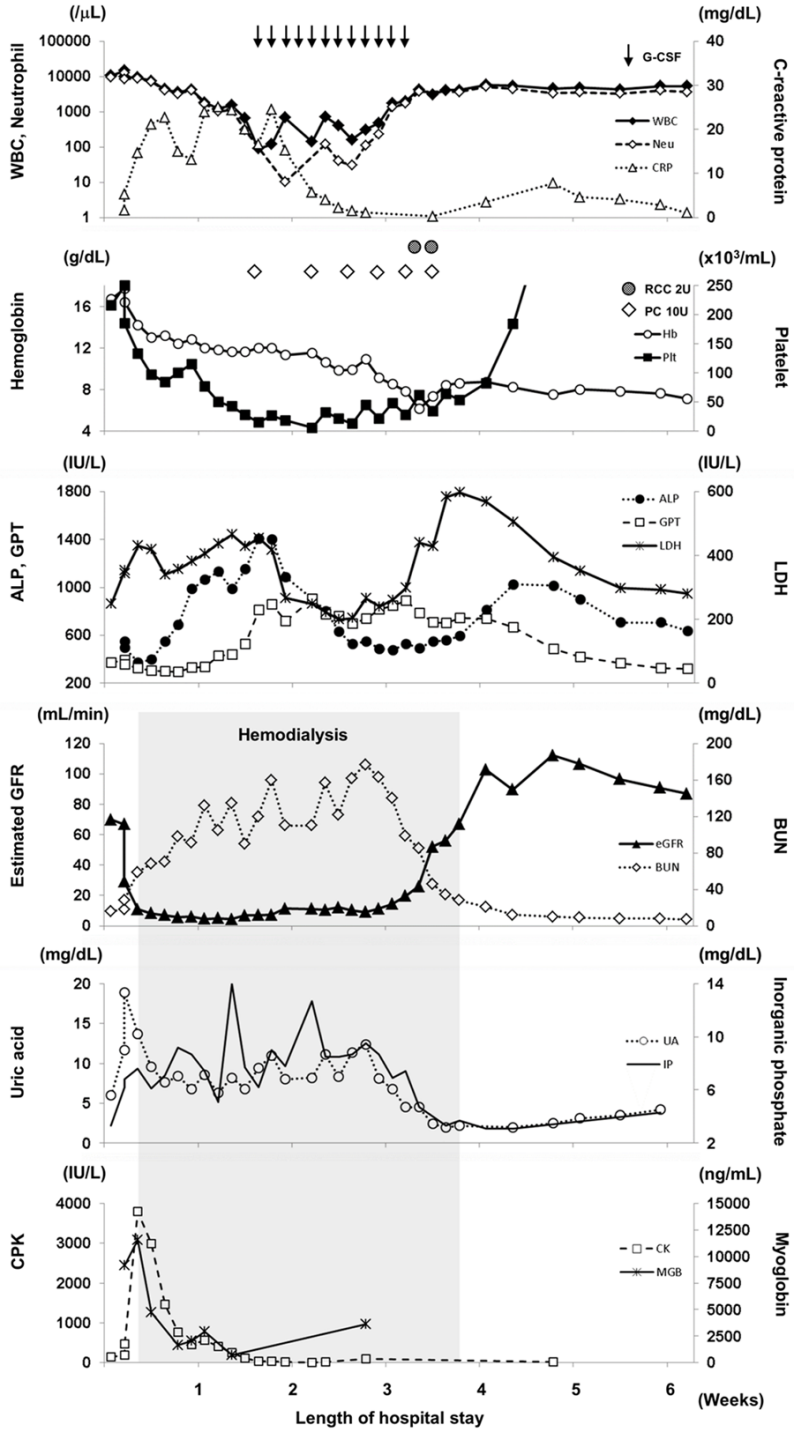

Figure 1. Clinical course of the patient.

severe vomiting and hematemesis due to accidental ingestion of approximately 1 g/kg EMS. We performed gastric lavage. Approximately four hours after intake, he developed repeated grand mal seizures, which were resistant to sufficient quantities of diazepam, phenytoin, phenobarbital, and midazolam. For this refractory status epilepticus, we induced a therapeutic coma using a continuous infusion of propofol and vecuronium bromide; the convulsions were suppressed but not completely eliminated. In addition to these drugs, the combined use of sodium valproate and carbamazepine with therapeutic drug monitoring had little effect on his status. Head computed tomography revealed no abnormal findings; head magnetic resonance imaging and a lumber puncture test could not be performed because of his unstable vital signs.

The clinical course of the blood examinations (**Figure 1**) showed marked hyperuricemia (uric acid, 18.4 mg/dL), hyperammonemia (243 μg/dL), and metabolic acidosis (arterial blood pH, 7.051; pCO_2, 44.2 torr; HCO_3, 11.7 mmol/L; anion gap, 38.3) the day after ingestion; subsequently, hyperphosphatemia (up to 14 mg/dL), severe acute renal failure (serum creatinine, up to 11.59 mg/dL), and hyperkalemia (up to 6.3 mEq/L) occurred. Blood glucose levels were 200-300 mg/dL. At the same time, serum creatine phosphokinase (CPK) and myoglobin peaked at 3800 IU/L and 11550 ng/mL, respectively. Urinary protein was >1000 mg/dL, and the urinary alpha 1 microglobulin level was 27.7 mg/L (normal range, <15.5 mg/L). Gross pigmenturia with hematuria was observed, but urine myoglobin estimation could not be completed. He required hemodialysis from the second hospital day. Elevated liver enzymes, hyperbilirubine-

mia, and high C-reactive protein levels were also observed. Infection was not detected by blood culture or imaging.

Within a week, hair loss and severe pancytopenia developed, the latter evidenced by the following: white blood cells, 90/μL; red blood cells, 1.92×10^6/μL; hemoglobin, 6.1 g/dL; and platelets, 15000/μL. Bone marrow aspirate showed markedly hypocellular marrow in all lineages and no hemophagocytic cells. Chromosomal analysis of the bone marrow showed a normal karyotype. Because we could not predict the length and depth of the nadir, we administered empiric prophylaxis with an antibiotic (cefepime) and antifungal drug (micafungin), based on the recommended management for hematopoietic stem cell transplantation. In addition to blood transfusion therapy, granulocyte-colony stimulating factor (G-CSF) was also administered. Fortunately, his peripheral neutrophil count recovered (up to 500/μL) at 22 days after the EMS ingestion. His seizures subsided, and he regained consciousness without neurological sequelae. On hospital day 27, hemodialysis could be stopped, and serum creatinine recovered to the normal range. Polyuria was subsequently observed, consistent with the diuretic phase of acute tubular necrosis, which resolved within weeks. It took approximately one month for normalization of liver enzymes and new hair growth. He was discharged from the hospital under close outpatient observation. Although he completely recovered from the acute toxicities, he died of a severe accidental injury two months later.

Discussion

To the best of our knowledge, this is the first report describing a human who was exposed to a massive dose of EMS and presented with a wide variety of acute toxicities. Because the oral bioavailability of EMS is almost 100% [7], the patient was exposed to a 1-g/kg bolus of EMS. A number of alkylating agents are used clinically as antitumor drugs; hematotoxicity is the most common adverse event. Therefore, it is not unexpected that a large EMS dose could cause pancytopenia. Similarly, high-dose (100 mg/kg) methyl methanesulfonate reportedly induces depression of erythropoiesis in mice [1]. Grade 4 hematological adverse events, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, are often managed with several supportive therapies such as blood transfusion, G-CSF administration, and prophylaxis for bacteria and fungi; the choice depends on the risk factors [8, 9]. Therefore, it was possible to successfully treat the present case with these palliative treatment options.

Busulfan, an alkylating antitumor drug for myeloid malignancy, is known to cause seizures when used in high doses as the conditioning regimen for hematopoietic stem cell transplantation [10]. Although the detailed mechanism has not been reported, it is assumed that the neurotoxicity is caused by blood-brain barrier (BBB) permeability [11]. Although it is not known if EMS can permeate the BBB, EMS is liposoluble, and the ability to pass through the blood-testis barrier has been reported [12]. Therefore, EMS might be able to cross the BBB and damage brain cells.

To reduce patient morbidity and mortality, status epilepticus requires emergent treatment such as benzodiazepines, phenytoin, phenobarbital, or valproate sodium. When the condition is refractory to these treatments, the guidelines for status epilepticus recommend proceeding with critical care treatment using a continuous infusion of the combination of midazolam, propofol, and pentobarbital [13]. At present, there are insufficient data to suggest which of these drugs is the preferred agent [14]. Pentobarbital might have better success in acutely controlling refractory status epilepticus than midazolam, but might have more adverse effects [15]. In our case, midazolam had little effect, while propofol suppressed the seizures, resulting in complete recovery.

Because EMS also alkylates nucleic acids in the liver and kidney, it could have directly caused the nephrotoxicity, hepatotoxicity, and inflammatory status [16]. However, the presentation with severe, refractory seizures and elevated serum CPK and myoglobin levels in the early clinical course might be explained by rhabdomyolysis secondary to muscular hyperactivity, as previously reported [17, 18].

The diagnosis of rhabdomyolysis is usually straightforward, based on the typical clinical symptoms of myalgia, weakness, and myoglobinuria (tea-colored urine). Elevated serum CPK

is the most sensitive indicator and is used as a standard laboratory finding for diagnosis [19]. In acidic urine, myoglobin dissociates into non-toxic (globin) and toxic (ferriheme) components. Ferriheme increases the level of oxidative free radicals, resulting in further damage to the renal parenchyma [20]. However, no single parameter has been established to predict the risk of acute kidney injury [21]. As our patient immediately developed concomitant elevation in serum CPK and creatinine, it was difficult to predict acute renal injury. Treatment for rhabdomyolysis consists of aggressive hydration, urinary alkalization with sodium bicarbonate or sodium acetate, or mannitol to promote diuresis to avoid acute kidney injury; however, there is limited evidence to support these choices [22]. Once acute renal failure occurs, dialysis has shown limited capacity to remove circulating myoglobin [19]. Continuous hemofiltration using a super high-flux membrane with a larger pore size can clear myoglobin from the serum [23] and might provide a treatment modality for progression. However, albumin leakage is a reported adverse event that should be rigorously addressed with albumin supplementation [24].

Propofol can also cause rhabdomyolysis as well as metabolic acidosis, cardiac dysfunction, hypertriglyceridemia, and renal failure (also known as propofol-infusion syndrome [PRIS]). The first large, prospective study investigating the development of PRIS in intensive care patients who were administered a propofol infusion for >24 hours indicated that the total cumulative dose might be a good predictor of PRIS [25]. In the present patient, we highly suspected secondary rhabdomyolysis due to severe status epilepticus; however, it is possible that propofol worsened the nephrotoxicity. With suspicion of PRIS, pentobarbital would be a better antiepileptic drug choice for status epilepticus accompanied by rhabdomyolysis.

In conclusion, a massive dose of EMS induces various adverse events as a result of acute toxicity including severe refractory status epilepticus, rhabdomyolysis, and pancytopenia. Excessive EMS toxicities requires multimodal treatment and can be reversed with appropriate palliative therapies. Because the present patient died shortly after hospitalization, we were not able to evaluate the genotoxicity at later stages.

Disclosure of conflict of interest

None.

Abbreviations

WBC, white blood cells; G-CSF, granulocyte-colony stimulating factor; Neu, neutrophil; CRP, C-reactive protein; RCC, red cell concentrates; PC, platelet concentrates; Hb, hemoglobin; Plt, platelet; ALP, alkaline phosphatase; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; GFR, glomerular filtration rate; eGFR, estimated GFR; BUN, blood urea nitrogen; UA, uric acid; IP, inorganic phosphate; CPK, creatine phosphokinase; MGB, myoglobin.

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