Death by Hand Sanitizer: Syndemic methanol poisoning in the age of COVID-19

Sarah Denise Holzman, Jaiva Larsen, Ramandeep Kaur, Geoffrey Smelski, Steven Dudley & Farshad Mazda Shirazi

Abstract

Background:

The advent of COVID-19 increased attention to hand hygiene in prevention of disease transmission. To meet the increased demand for hand sanitizer during the pandemic, the US FDA issued an Emergency Use Authorization allowing new manufacturers and importers to enter the market. Some of the newly introduced hand sanitizer products contained methanol in lieu of ethanol or isopropanol. We describe five patients with fatal methanol poisoning resulting from hand sanitizers improperly containing methanol.

Case Summary:

Comparing a 5-month period from 2019 to the same time frame in 2020, the Arizona Poison and Drug Information Center has seen an increase of 124% in exposures to hand sanitizer. Of these cases, 28% involved methanol-contaminated hand sanitizer. Five of these patients died from methanol poisoning. All five cases had similar clinical features with severe high anion gap metabolic acidosis and, in four cases, elevated osmolal gap. Methanol concentrations were consistently very elevated, but these results were not available before the patients succumbed. Four of the patients received fomepizole and adjunctive care. Two patients received emergency extracorporeal therapy. All five died despite maximal treatment efforts.

Conclusion:

During the pandemic in 2020, there was a proliferation of alcohol-based hand sanitizers which contained methanol. Exposure to these products, which failed to meet regulatory standards, led to increased harm and death. Challenges to treatment of methanol poisoning, especially in rural areas, include lack of access to timely laboratory measurement of methanol concentrations and lack of available emergency hemodialysis without transfer of the patient.

Introduction

In early 2020, SARS-CoV-2 emerged in the United States [1]. In response to the pandemic, public health authorities established guidelines to curtail transmission. As part of the push for hand hygiene, if soap and water were not readily available, the use of ethanol- or isopropanol-based hand sanitizer was advised [2,3]. The supply of these items at the onset of the pandemic, however, was insufficient for the increased demand.

Consequently, the US FDA issued an Emergency Use Authorization (EUA) permitting new manufacturers and importers to produce and import hand sanitizer for the length of the pandemic [4]. Some of the hand sanitizers developed and imported under the EUA have been found to contain concentrations of ethanol and isopropanol lower than those recommended by public health guidelines (60-95% v/v alcohol), or to contain methanol or 1-propanol concentrations that exceed “impurity limits” under the temporary FDA policy (630 ppm for methanol and 1000 ppm for 1-propanol) [4-9]. As the list of methanol-contaminated hand sanitizers grows in the United States, methanol poisoning during the COVID-19 pandemic has become syndemic with SARS-CoV-2 infection. Figure 1 shows a timeline of these events [4-9].

The Arizona Poison and Drug Information Center (APDIC) provides phone consultation services 24 hours per day 365 days per year to 14 of the 15 counties in Arizona. From May 1 to October

14, 2020, APDIC consulted on 132 patients with hand sanitizer exposure. Of these cases, 37 involved methanol contamination. Five of these patients died. In comparison, from May 1 to October 14, 2019, APDIC consulted on 59 hand sanitizer exposures. None of the 2019 cases involved methanol contamination, and there were no deaths. Here we present a case series of five patients whose ingestion of methanol, during the COVID-19 pandemic, resulted in fatal outcome.

Cases

See corresponding Tables 1 and 2.

Patient A

In May 2020, APDIC received a call from an emergency department (ED) regarding a 49-year-old male who was ataxic with vision loss. He reported that he had ingested up to a gallon of hand sanitizer after a breakup with his girlfriend. His vital signs on presentation were blood pressure (BP) 176/84 mm Hg, heart rate (HR) 111 beats per minute (bpm), respiratory rate (RR) 26 breaths per minute (br/min), temperature 35.6 °Celsius (°C). Laboratory investigations revealed a severe metabolic acidosis (serum bicarbonate <5 mmol/L). Serum ethanol concentration was negative. Within an hour after his arrival, he started having seizures. As he was being transferred to a critical care room, he became hypotensive, then pulseless. He developed *torsades des pointes* and ventricular fibrillation. He died approximately 2 hours after presentation.

Patient B

In June 2020, a 36-year-old male had been on a drinking binge of whiskey and hand sanitizer for several days. After feeling unwell for at least one day, he asked his mother to call EMS. He then

went outside, collapsed, and was found unresponsive in the yard. On arrival to the ED, he was unresponsive, with respiratory depression, fixed and dilated pupils, and was producing copious thick oral secretions. Initial vital signs were BP 130/78 mm Hg, HR 66 bpm, RR 8 br/min, O2 saturation around 85% on room air, temperature 34.5 °C. He was intubated. Laboratory values showed severe metabolic acidosis (pH 6.68) and a calculated osmolal gap of 141 mOsm/kg H_2O. Ethanol was undetectable. He received fomepizole, folic acid, thiamine, and sodium bicarbonate (NaHCO3), and was transferred to a tertiary health care facility (HCF). In the ICU, fomepizole, folic acid, thiamine, and NaHCO3 were continued, and pyridoxine was added. On hospital day 3, a nuclear medicine perfusion study revealed no intracranial blood flow, and he was pronounced dead. His serum methanol concentration, drawn approximately 23 hours after he presented to ED, was 165 mg/dL. This result became available after his death.

Patient C

In June 2020, a 53-year-old male developed headache, vomiting, and blindness, after drinking a mixture of vodka and hand sanitizer 24 hours prior to his ED presentation. On presentation, he was moaning and unable to follow commands. His vital signs were BP 94/58 mm Hg, HR 101 bpm, RR 18 br/min, O2 saturation 94%, temperature 36.5 °C. Within an hour of his arrival, he developed cardiopulmonary arrest. He was resuscitated and intubated, developed bradycardia and hypotension, and continued to require vasopressors.

Initial laboratory results revealed severe metabolic acidosis (pH 6.62) and an osmolal gap of 98 mOsm/kg H_2O. His ethanol concentration was 34 mg/dL. Based on these values, along with his visual symptoms and altered mental status, there was concern for methanol poisoning. He received fomepizole, folic acid, thiamine, pyridoxine, NaHCO3, and was transferred to a tertiary HCF.

In the ICU, he remained unresponsive, hypotensive, and tachycardic. He continued to receive vasopressors for blood pressure support and NaHCO3 for treatment of metabolic acidosis. Fomepizole, pyridoxine, and thiamine were continued, folinic acid was given in place of folic acid, and continuous renal replacement therapy (CRRT) was instituted. On Day 6, MRI showed hypoxic ischemic injury with diffuse cerebral edema, hemorrhage, and herniation. He was pronounced dead.

His family identified the hand sanitizer he drank as "Bersih hand sanitizer," which was found to contain methanol [9].

Patient D

In June 2020, a 47-year-old female was found in her home unconscious and unresponsive. She was last seen awake the night before. Near her was an empty bottle of insect repellent (active ingredient N, N-Diethyl-meta-toluamide 7.0%), and a bottle of hand sanitizer was missing. Per family report, she periodically drank hand sanitizer and rubbing alcohol when ethanol was not available. On arrival to the ED, her vital signs were BP 147/82 mm Hg, HR 92 bpm, RR 6 br/min, O2 saturation 90%, temperature 36.1 °C. Laboratory investigations revealed a severe metabolic acidosis (pH 6.70) and an osmolal gap of 132 mOsm/kg H_2O. Ethanol was undetected. She was intubated, empirically started on fomepizole, and hemodialyzed. She also received folic acid, thiamine, pyridoxine, and NaHCO3. During the placement of the dialysis catheter, she experienced a generalized tonic-clonic seizure. Head CT, eight hours after arrival to the HCF, showed diffuse anoxic injury with cerebral edema, herniation, and hemorrhage. On Day 2, nuclear medicine imaging revealed lack of cerebral blood flow. She was transitioned to DNR

status, and she died. Her serum methanol concentration, 278 mg/dL, was drawn when she presented to the ED. The result became available after her death.

Patient E

In September 2020, a 41-year-old female came to the ED due to severe abdominal pain and vomiting after reportedly drinking “vodka” for several days. On presentation she was agitated and became increasingly combative. Her initial vital signs were BP 136/99 mm Hg, HR 124 bpm, RR 20 br/min, O2 saturation 96%, temperature 36.3 °C. After the administration of an anti-emetic, sedatives, and IV fluids, she appeared to be resting comfortably. Approximately 3 hours after arrival, her laboratory values revealed a profound metabolic acidosis (pH <6.82). Serum ethanol was reported as negative. Within the next hour, she developed agonal respirations. As she was being prepared for intubation, she developed cardiac arrest. During resuscitation she experienced multiple seizures. After return of spontaneous circulation, she received fomepizole, NaHCO3 for her metabolic acidosis, vasopressors for blood pressure support, and she was transferred to a tertiary HCF.

In the ICU, she was unresponsive and exhibited rhythmic shaking movements of the right side of her body. Fomepizole and NaHCO3 were continued, and folinic acid, pyridoxine, and thiamine were added. CT showed diffuse cerebral edema.

On Day 2, nuclear medicine imaging showed absence of blood flow to the brain. Medical intervention was discontinued, and she died. Her methanol concentration, drawn on arrival to the ED, was 309 mg/dL. This result became available after her death.

Discussion

Exposure to methanol-contaminated hand sanitizer may occur by accident (especially in children with exploratory ingestions), by people drinking hand sanitizer as an ethanol-substitute, and by people with intentions of self-harm. Of the five patients in this case series, two appear to have ingested hand sanitizer as an ethanol-substitute. For the other three, the motivation is less clear, and suicidal intent is possible. The availability of hand sanitizer, and the expectation that it is a source of "alcohol," resulted in these patients consuming a substance that carried a much greater risk than they could have anticipated.

Predictors of lethal outcome in methanol toxicity include profound metabolic acidosis, respiratory failure, coma, seizure, or delay in treatment [10-14]. All five patients in this case series presented with effects that signaled poor outcome. All of them had a severe metabolic acidosis, with serum bicarbonate values of ≤5 mmol/L, and serum pH of <6.82 in the four patients in whom blood gas was obtained. The profound metabolic acidosis suggests that significant metabolism of methanol to formic acid had already taken place prior to presentation.

Two of the five patients were unresponsive prior to arrival to the ED, and the other three deteriorated, and became unresponsive soon after presentation. Three experienced seizures in the ED. Three developed cardiopulmonary arrest in the ED. All five of them required intubation in the ED, although one died before intubation.

In all four patients with a measured osmolality, both the osmolal gap and anion gap were extremely high. An elevated osmolal gap, which indicates the presence of an osmotically active substance, can be useful in establishing the presence of a toxic alcohol. An osmolal gap range of (-)10 to 20 mOsm/kg H_2O has been suggested as "normal" [15]. Clinicians vary in their threshold for concern with osmolal gap elevations, but an osmolal gap >25 mOsm/kg H_2O is generally considered clinically significant [10,16,17]. Limitations of the osmolal gap include the

variability in the formula used to calculate the gap, the wide variability for baseline “normal” gap among individuals, and the elevation in gap due to other medical conditions [18-22]. Additionally, as toxic alcohols are metabolized, the osmolal gap is expected to decline rendering it insensitive to a late-presenting methanol intoxication [18-22]. Since timely methanol concentrations are usually unavailable, clinicians must assess the poisoning based upon clinical history, physical findings, the anion gap, and the osmolal gap [16-22].

In this case series, methanol concentrations were reported for three patients, but results were not available until postmortem. A methanol concentration of 40-50 mg/dL produces serious toxicity [18,23]. The methanol concentrations obtained for these patients, ranging from 165 to 309 mg/dL, were well above the threshold for detrimental effects.

Four of the patients received fomepizole, a competitive alcohol dehydrogenase inhibitor used to prevent the metabolism of ethylene glycol and methanol to their respective toxic metabolites. Indications for its use in methanol poisoning include an anion gap metabolic acidosis, elevated osmolal gap, visual changes, a clinical suspicion of methanol ingestion, or a serum methanol concentration of ≥20 mg/dL [18,19,24-26]. Ethanol, which is also a competitive inhibitor of alcohol dehydrogenase, can be used if fomepizole is not available [10,18,19,26,27].

The other effective treatment for methanol poisoning is extracorporeal therapy. One patient received hemodialysis, and another received CRRT after transfer to a tertiary HCF. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommends hemodialysis for any of the following: coma, seizures, new onset of visual impairment, blood pH ≤7.15, refractory metabolic acidosis, anion gap >24 mmol/L, and various thresholds based on serum methanol concentrations [28]. Both patients met the criteria based on unresponsiveness, pH ≤7.15 and

anion gap >24 mmol/L. One patient also had visual deficits, and the other also experienced seizures.

Four patients received NaHCO3 to correct severe metabolic acidosis. The reversal of acidemia with NaHCO3 may also positively impact the conversion of formic acid to formate, and increase the elimination of formate [18,19,27]. These four patients also received folinic or folic acid, which promotes the metabolism of formic acid to water and carbon dioxide [18,27,29]. Folinic acid is preferred over folic acid, as it is the metabolically active form [18,29].

Despite receiving intensive therapies, none of these patients survived. All the fatalities occurred in patients that presented either unresponsive or in extremely severe conditions, likely contributing to the lack of treatment success.

Four of the patients in this case series had a history of ingesting hand sanitizer. The brand Bersih was identified for one patient. Although a methanol concentration was not obtained for this patient, this brand of hand sanitizer product was subsequently recalled due to methanol contamination. The source of methanol for the fifth patient was undetermined. In the midst of this outbreak of methanol poisoning, ingestion of hand sanitizer was strongly suspected. In all five cases, the ethanol concentrations were low or negative. The isopropanol concentrations, available for four patients, were also negative. This suggests that the products ingested contained little or none the FDA-approved active ingredients for hand sanitizers.

Four of these exposures occurred in regions of the state where consumption of alcoholic beverages is prohibited. With increased efforts to make alcohol-based hand sanitizer available during the pandemic, the relatively low cost of these products, and the expectation that hand

sanitizer is a highly concentrated ethanol- or isopropanol-based product, consumption of hand sanitizer is understandably appealing for someone seeking an alternative source of ethanol.

Conclusion

We present five severe and rapidly fatal methanol poisonings in the setting of ingestion of hand sanitizers improperly containing methanol. Laboratory findings suggesting severe methanol poisoning include high anion gap metabolic acidosis and elevated osmolal gap. Timely methanol concentrations are seldom available, so treatment decisions cannot await these results. Clinical findings include altered mental status that is not explained by ethanol, other drugs, or trauma. Visual deficit, seizure, and coma may occur. Clinical treatments include fomepizole (or ethanol if fomepizole is not available) and earliest possible hemodialysis.

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Figure 1. Timeline 2020

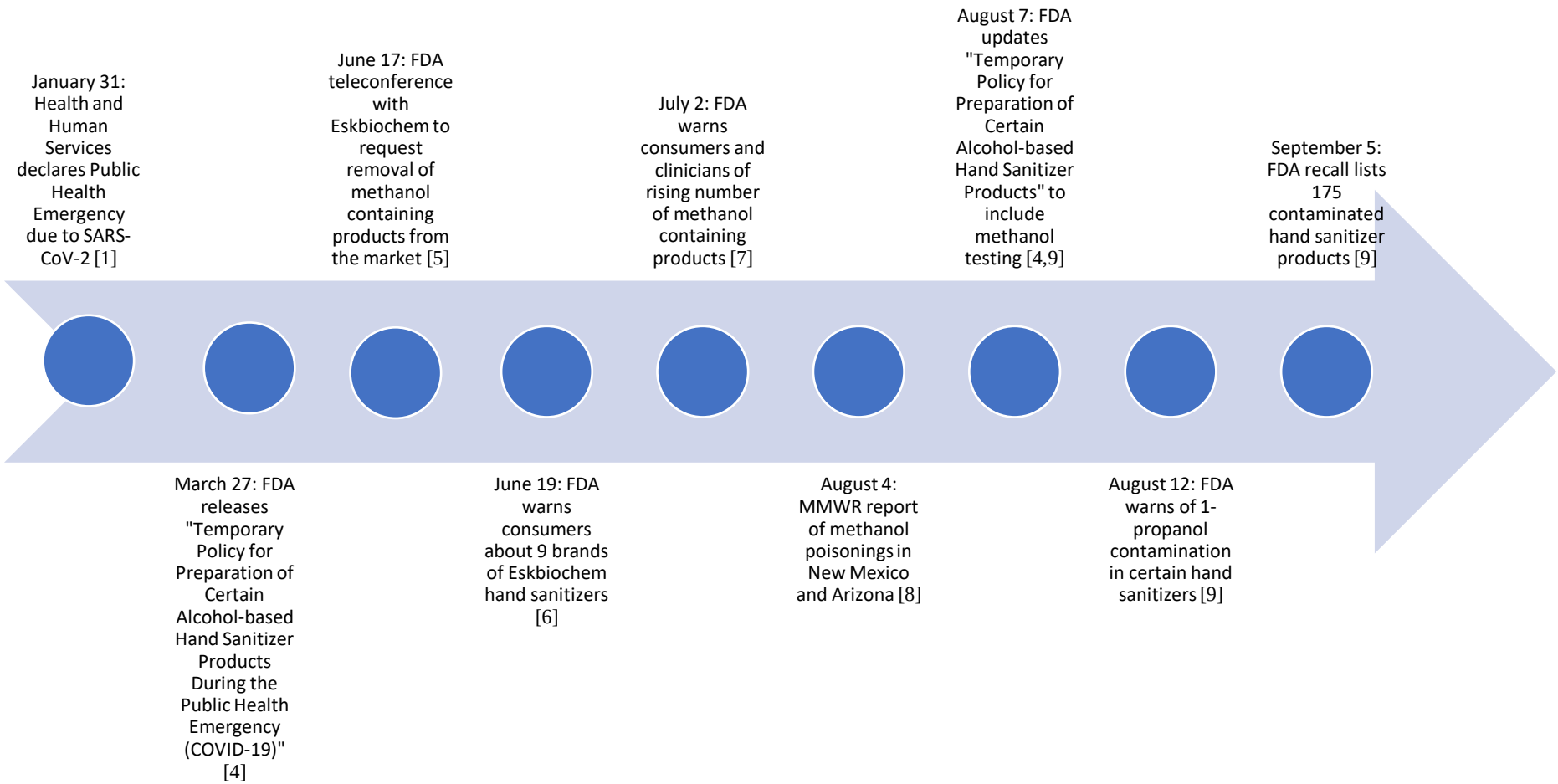

Table 1. Patient Background and Clinical Course

Patient	**A**	**B**	**C**	**D**	**E**
Gender	M	M	M	F	F
Age (years)	49	36	53	47	41
Past medical history	Alcohol use disorder, anxiety, depression	Alcohol use disorder, coarctation of the aorta	Alcohol use disorder	Alcohol use disorder, depression, hypertension	Alcohol use disorder, post-traumatic stress disorder, gastroesophageal reflux disease
Product consumed	Patient reported hand sanitizer, unknown brand	Family reported whisky and hand sanitizer, unknown brand	Family reported vodka and hand sanitizer, Bersih brand [9]	Family reported DEET-based insect repellent and hand sanitizer, unknown brand	Patient reported "vodka"
Patient intent	Uncertain: intentional self-harm vs. misuse/abuse	Apparent misuse/abuse	Apparent misuse/abuse	Uncertain: intentional self-harm vs. misuse/abuse	Uncertain: intentional self-harm vs. misuse/abuse
Effects prior to arrival to HCF	Ataxia, visual deficit	Felt "hung-over," unresponsive	Headache, nausea, vomiting, visual deficit	Unresponsive	Abdominal pain, vomiting
Effects on presentation to HCF	Seizures, hypotension, pulseless, *torsades des pointes*, ventricular fibrillation	Unresponsive, respiratory depression, fixed and dilated pupils, thick oral secretions	Minimally responsive, cardiopulmonary arrest, ventricular fibrillation, hypotension, bradycardia, atrial fibrillation	Unresponsive, seizures	Agitation, cardiopulmonary arrest, seizures

Table 2. Laboratory values on presentation (unless otherwise specified)

Patient	A	B	C	D	E
Serum methanol (mg/dL)	Not available	165[1]	Not available due to insufficient sample quantity	278	309
Serum ethanol (mg/dL)	Negative	Negative	34	Negative	Negative
Serum isopropanol (mg/dL)	Not available	Negative	Negative	Negative	Negative
Serum acetone (mg/dL)	Not available	Negative	Negative	Negative	Negative
Osmolal Gap (mOsm/kg H_2O)	Not available	141	98	132	92[2]
Arterial blood pH (unless noted)	Not available	6.68	6.62	6.70	<6.82[3]
PCO2 (mm Hg)	Not available	33.9	67.4	31.5	19.2[4]
Serum bicarbonate (mmol/L)	<5	<5	5	<5	<5

[1]Drawn 23 hours post-presentation to ED. [2]Calculated with laboratory values drawn 10.5 hours post-presentation. [3]Venous blood pH. [4]PCO2 venous blood