Toxin-induced Malignant Hyperthermia?

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Triclosan (5-chloro-2-[2, 4-dichlorophenoxy] phenol) is an antibacterial and antifungal agent found in numerous consumer products. It has been in use for more than four decades and is present in soaps, shampoos, deodorants, toothpastes, mouth washes, and cleaning supplies [1]. Presently, triclosan is being incorporated into an increasing number of products including toys, bedding, clothes, and trash bags [1]. On contact, triclosan penetrates the skin and enters the bloodstream. Due to its high hydrophobicity, triclosan accumulates in fatty tissues and is found in human samples (urine, breast milk, and serum) [1]. At high concentrations, triclosan acts as a biocide with multiple cytoplasmic and membrane targets [1].

Cherednichenko and colleagues [2] found that triclosan impaired excitation-contraction coupling and Ca^{+2} dynamics in striated muscle of mice. Based on previous receptor-based screens, triclosan has the potential to alter the activity of type 1 and type 2 ryanodine receptors (RyR1 and RyR2) [3]. These intracellular channels mediate the release of Ca^{+2} from the sarcoplasmic reticulum, which is necessary for excitation-contraction coupling in skeletal and cardiac muscles. Mutations in the RyR1 gene are linked to dysregulated Ca^{+2} homeostasis and disorders such as malignant hyperthermia (MH). MH is induced by exposure to succinylcholine or potent inhalation anesthetic agents in genetically susceptible individuals. It is an extreme hypermetabolic state, which manifests with high core temperature, tachycardia, lactic acidosis, massive rhabdomyolysis, acute kidney and liver injury, coagulopathy, and eventually hemodynamic collapse. Three patients presented to our intensive care unit (ICU) with MH-like symptoms; however, no exposure to any of the triggering agents was reported.

PATIENT DESCRIPTION

Following institutional review board approval (IRB no. 0192-14-TLV), we examined the records of three patients admitted to our ICU between May and June 2013 with clinical presentation similar to MH. Informed consent was waived due to the anonymous retrospective collection of data.

Within a 1-month period, three middle aged male patients (33–47 years of age) were admitted to our ICU shortly following intravenous (IV) injection of party-drugs containing cathinones, which were purchased in the same area in the city of Tel Aviv. They presented with tachycardia, hypotension, high temperature (≥ 40°C rectal), altered mental status (Glasgow Coma Scale < 14), massive rhabdomyolysis (creatine phosphokinase > 5,000 U/L), acute kidney injury (creatinine > 132.6 µmol/l), prolonged coagulation profile (international normalized ratio > 1.2), thrombocytopenia (platelets < 150,000 103/µl), lactic acidosis (lactate > 0.22 mmol/l and pH < 7.35), and elevated liver enzymes (alanine transaminase > 40 U/L) [Table 1]. Patients did not display muscle rigidity or extrapyramidal signs. None of the patients had a past history of diabetes, muscular dystrophy, or myotonia. None had exercised or had been exposed to extreme heat.

Blood, sputum, and urine cultures were taken from all patients on arrival to the emergency department. Rapid urine toxicology test was negative for opioids, cocaine, benzodiazepines, amphetamines, cannabinoids, and NMDA derivatives. The urine sample of one patient was sent to a special toxicology analysis in another medical facility.

On arrival at the ICU patients were intubated, ventilated, and sedated with either IV fentanyl or remifentanil. Active cooling was than initiated. The patients received two liters of cold (4°C) normal saline. Their clothes were removed, and they were wrapped in cold wet blankets. This treatment failed to achieve the target temperature (core temperature 36.0–36.5°C) in one patient so we applied the CritiCool™ microprocessor-controlled temperature management unit (MTRE®, Or Akiva Industrial Park, Or Akiva, Is-

Table 1. Laboratory data at ICU admission

Patient no.	Creatinine (µmol/l)	Platelets (103/µl)	ALT (U/l)	CPK (U/l)	INR	pH	Lactate (mmol/l)
1	369.5	20	591	77,193	3.61	7.3	0.44
2	172.3	80	532	73,365	1.3	7.34	0.33
3	184.7	53	102	9,082	1.51	7.3	0.33

ALT = alanine transaminase, CPK = creatine phosphokinase, ICU = intensive care unit, INR = International normalized ratio

rael) with efficacious response. Normothermia was achieved within 2 to 4 hours.

All patients required large volumes of fluids and vasopressor continuous support to achieve mean arterial blood pressure of 65 mmHg. After obtaining cultures, they were given ceftriaxone as empiric antibiotics. All cultures eventually were found to be negative. The three patients developed severe rhabdomyolysis and, as a result, acute kidney injury. Fluids, bicarbonate, and mannitol were given to promote diuresis. One patient required several hemodialysis treatments, but eventually kidney function recovered before discharge in all patients. Lactate levels decreased toward normal levels within 3 to 6 hours following initiation of supportive treatment. None of the patients required prolonged intubation, with maximal ventilation time of 2 days. No significant pulmonary complications, such as acute respiratory distress syndrome, were observed.

On regaining consciousness, all three patients admitted to having injected Hagigat (Illicit cathinone) intravenously prior to admission. The drugs were purchased at the same place within a relatively short time. All patients survived without sequels and were discharged to the ward within 4 to 8 days. Several days after discharge, the toxicology analysis of the urine for special toxins confirmed that the urine contained large quantities of triclosan, which was used as a solvent during drug-preparation. No other substances were found.

COMMENT

Evaluation of patients admitted to the ICU with symptoms of obscure origin is not uncommon and is always challenging. Hereby we present the story of three patients who were admitted to our ICU with clinical picture resembling MH, nevertheless none of these patients have been exposed to conditions or circumstances that are known to induce MH. Upon regaining consciousness, all patients acknowledged injecting cathinone-based street drugs intravenously shortly before becoming symptomatic. The drugs were marketed under the name *Hagigat* and were illegally manufactured in home labs and sold as liquid-containing capsules made for IV injection. All patients purchased the drugs at the same place in Tel Aviv during the same time period.

An average of at least 3 to 4 patients are admitted to our ICU every month due to street drug toxicity, mainly cathinone-based, homemade drugs. The active substances in the drugs differ in quantity and composition, and numerous derivatives of cathinones are used to create tablets, capsules, powders, and liquid formulae for ingestion or IV injection. Numerous solvents and unknown chemicals are added to the active substance to allow IV injection, including triclosan, obviously without any supervision. The drugs are marketed under different names.

Cathinone-based drugs are usually made from khat leaves, of the plant Catha Edulis, which are natural stimulants and aphrodisiacs. The plants grow mostly in east Africa and the Arab peninsula [4]. In those areas, chewing khat leaves is very popular, but since the consumed active substance is minimal, toxicity is very rare. If purified cathinones are consumed in large quantities, they can cause severe toxicity. Bentur and colleagues [5] examined the records of 34 patients aged 16–54 years with cathinone toxicity. The authors found that the most common clinical features of cathinone toxicity were headache, nausea and vomiting, hypertension, tachycardia, dyspnea, chest pain, and myalgia. Severe complications included myocardial infraction, pulmonary edema, and intracerebral bleeding, even in young patients [5].

Cathinone-based drugs are usually consumed by ingestion, smoking, or sniffing. To maximize its psychogenic influence, some consumers prefer to inject it intravenously, even with formulae that are not originally designed for IV injection. Users who inject the drug intravenously are more prone to developing severe cathinone toxicity, as large quantities of active substance are quickly delivered to the bloodstream. This method may end in life-threatening reactions to the solvents or other added chemicals.

In the present series, all patients injected cathinone-based drugs (marketed under the name *Hagigat*) intravenously and presented with MH-like syndrome. To the best of our knowledge, cathinone toxicity per-se was not described as causing this clinical manifestation before, although most of the earlier reports of cathinone toxicity [5] were of patients who ingested or smoked the substance. We previously admitted patients who injected Hagigat or other cathinone-based street drugs to the ICU in our medical facility; however, they presented with other clinical manifestations including psychosis, agitation, hypertension, and tachycardia but not the MH-like syndrome. We suspected that in these patients the toxidrome was caused by a new solvent preparation. Therefore, a urine sample from one patient was sent to a specialized toxicology laboratory for analysis with gas chromatography/mass spectroscopy technique. The urine was found to have large quantity of triclosan, which was used as a solvent during drug-preparation.

The literature is lacking any description of the symptomology following IV administration of triclosan. The only report we found of systemic administration of triclosan was by Cherednichenko and colleagues [2] who described the effects of intraperitoneal triclosan on the cardiac and skeletal muscles of mice. The authors found an acute and significant hemodynamic compromise within 10 minutes of injection of triclosan in a dose-dependent manner, including reduced cardiac output (up to 25 ± 15%) and reduction in the maximum time-derivative of the left ventricular pressure development. In the skeletal muscle, the animals treated with triclosan had a mean decrease of 18% in grip strength. Although the investigators did not report MH-like phenomena in the mice injected with intraperitoneal triclosan, the mech-

anism of action of triclosan on the type 1 and type 2 ryanodine receptors activity resembled that of MH progress.

If indeed the MH-like syndrome was the result of triclosan toxicity mediated through interference with the ryanodine receptors activity, then perhaps treatment with dantrolene, which is the first line therapy in MH, could have reversed the toxidrome. There are no available data on this treatment option in this circumstance. Moreover, dantrolene therapy is usually not recommended in other clinical syndromes resembling MH, such as heat stroke or serotonin syndrome, as it did not prove to be efficacious.

CONCLUSIONS

MH-like syndrome may result from triclosan poisoning. Prompt recognition of this entity is essential to avoid unnecessary investigations and significant morbidity and mortality.

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One may have a blazing hearth in one's soul, and yet no one ever comes to sit by it.
Vincent van Gogh (1853–1890), Dutch Post-Impressionist painter

What is the opposite of two? A lonely me, a lonely you.
Richard Wilbur (1921–2017), American poet and literary translator

Capsule

Yellow fever virus treatment

Yellow fever virus (YFV) is becoming a threat to global health because of changes in the environment. A live attenuated vaccine (YFV-17D) has been used for decades, but immunization coverage diminished in recent years because of concerns about adverse reactions, which has left many unvaccinated people in endemic areas vulnerable to infection. **Ricciardi** and colleagues characterized monoclonal antibodies (mAbs) that can neutralize YFV and prevent severe disease in animal models. They screened 37 YFV-specific mAbs isolated from vaccinated humans, of which two showed potent neutralization activity against a range of YFV isolates. Administration of a single dose of either mAb to YFV-infected hamsters or nonhuman primates protected against severe disease and death. These findings suggest that YFV mAbs may be a potential therapeutic treatment that could improve outcomes during outbreaks.

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Capsule

Blocking NS3–NS4B interaction inhibits dengue virus in non-human primates

Goethals and colleagues presented JNJ-1802, a highly potent DENV inhibitor that blocks the NS3–NS4B interaction within the viral replication complex. JNJ-1802 exerts picomolar to low nanomolar in vitro antiviral activity, a high barrier to resistance and potent in vivo efficacy in mice against infection with any of the four DENV serotypes. The authors demonstrated that the small-molecule inhibitor JNJ-1802 is highly effective against viral infection with DENV-1 or DENV-2 in non-human primates. JNJ-1802 has successfully completed a phase I first-in-human clinical study in healthy volunteers and was found to be safe and well tolerated. These findings support the further clinical development of JNJ-1802, a first-in-class antiviral agent against dengue, which is now progressing in clinical studies for the prevention and treatment of dengue.

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