

Bad news about an old poison. A case of nicotine poisoning due to both ingestion and injection of the content of an electronic cigarette refill

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Abstract

There are increasing concerns about the escalating use of electronic cigarettes (e-cigarettes). In particular, smokers have been advised by important agencies such as the US Food and Drug Administration about the potential harm to the health of these products, being now considered as drug delivery devices. The leading issues supporting this statement include the repeated inhalation of propylene glycol that is used as a diluent in refills, accidental poisoning, as well as evidence that e-cigarettes may promote continued smoking since their use may compromise quitting motivations. Some authors have minimized these risks, considering the potential advantages of these devices for public health. Here we describe the first case of nicotine poisoning due to both ingestion and intravenous injection of the content of an e-cigarette refill, incorrectly mixed with methadone, bottled in a generic vial.

Case Report

A 22 year-old girl, chronically assuming methadone for opioids addiction, has been admitted to our emergency department (ED) complaining for tachycardia, flushing, salivation and nausea. Her body weight was 47 kg. She reported to have mixed the residual content of an electronic cigarette (e-cigarette) refill (*i.e.* 10 mL of a 0.8% solution) with 60 mL of methadone, and to have bottled the mixture in a generic vial. She also admitted to have injected about 2 mL of the mixed solution, and to have intentionally ingested about 60 mL of it 2 h before ED visit. She was awake, tachycardic, and in good general conditions, pupils were myotic, there were many old venipuncture scars on her arms and legs. Her vital signs were: heart rate (HR) 115 beats per minute (bpm; sinus tachycardia at the ECG), arterial blood pressure (BP) 150/105 mmHg, body tem-

perature 36.8°C, and peripheral O₂ saturation (spO₂) 100% in ambient air. Orogastric lavage was promptly performed, and 50 g of activated charcoal followed by 30 g of magnesium sulphate were administered via orogastric tube. The toxicological standard panel used in our Hospital was performed, resulting positive for methadone, and negative for benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, opioids and ecstasy (MDMA). The patient was then monitored and kept under clinical observation. The symptoms and vital signs progressively improved, and nearly 3 h after admission the clinical condition was dramatically improved, with vital signs as follows: HR 82 bpm, arterial BP 105/60 mmHg, body temperature 36.7°C, and spO₂ 100%. She was discharged after a psychiatric consultation and addressed to the addiction services of our town.

The refill of the e-cigarettes was in the meantime brought to the ED, and the content was quantified in 18 mg of nicotine per mL of solution. It was then calculated that the patient had globally assumed about 36 mg of nicotine, 2-3 mg intravenously (*i.v.*), and 33-34 mg *per os*. The dose of methadone ingested was 60 mg, which corresponds to the usual dose assumed by the patient.

Discussion

Nicotine is a natural alkaloid derived from the dried leaves and stems of *Nicotiana tabacum* and *Nicotiana rustica*, where it is present in concentrations comprised between 0.5 and 8%.¹ The name is directly derived from that name of plants, which were originally classified by Jean Nicot de Villemain, the French ambassador in Portugal, who sent tobacco and seeds to Paris in 1560, and who promoted their medicinal use. Nicotine is a hygroscopic, oily liquid that is miscible with water in its base form. It is a potentially addictive drug used in cigarettes as well as in sniffing and chewing tobacco. Gums and patches, as well as the recently introduced e-cigarettes that are typically used for purpose of withdrawal from smoking, also contain nicotine. The oral bioavailability of nicotine is less than 20%, and absorption from the oral mucosa is the principal site of nicotine absorption in subjects who chew tobacco or nicotine gum.² Nicotine distributes extensively into body tissues with a volume of distribution ranging from 1.0 to 3.0 L/kg.² The median lethal dose (LD₅₀) of nicotine is 50 mg/kg for rats, and 3 mg/kg for mice, but 30 to 60 mg (*i.e.* nearly 0.5 to 1.0 mg/kg) can be a lethal dose for adult humans.³ The cigarettes typically contain 8 to 20 mg of nicotine depending on the brand, but smokers actually

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absorb only about 1 mg per cigarette.¹ At variance with cigarettes, many brands of cigars contain at least 10-20 times higher amount, in exceptional cases approximating 50 times.⁴ Nicotine mainly acts on the parasympathetic and sympathetic nervous system, where it binds to specific nicotinic acetylcholine receptors. The nicotine dose-response relationship is complex. Low doses stimulate neural systems, triggering central or peripheral nervous system stimulation with arousal and increase in HR and arterial BP, whereas higher doses produce an inhibitory effect acting through ganglionic blockade and thereby finally resulting in bradycardia, hypotension, and depressed mental status.^{1,5,6} Due to the remarkably low LD₅₀, nicotine can hence be considered one of the most toxic poisons, with very rapid onset of action despite a broad inter-individual tolerance to the toxic effects.⁷ Toxic symptoms might be observed with doses as low as 2-5 mg, and non-fatal cases of intentional or accidental nicotine poisoning have been reported in the current scientific literature.^{8,9} In mild nicotine poisoning the leading clinical signs and symptoms include nausea, headache and dizziness, along with the possible onset of vomiting and diarrhea. In more severe cases, abdominal pain, diaphoresis, weakness, confusion, seizures, and death due to respiratory muscle paralysis might develop. Cardiovascular signs of acute nicotine poisoning include tachycardia and hypertension at low doses, whereas bradycardia and hypotension occur more specifically with high doses.³ Although nicotine is one of the most toxic drugs of abuse, it rarely leads to fatalities.

Fatal poisoning from concentrated-nicotine solution and pesticides have been described,^{10,11} but only a few cases of fatal nicotine poisoning have been reported during the past 20 years.¹⁰⁻¹²

Acute nicotine poisoning caused by injection of nicotine solution is extremely rare. Hagiya *et al.* have recently described the case of nicotine poisoning due to intravenous injection of cigarette soakage in a nurse who soaked 20 cigarettes in 100 mL of tap water for 1 h, and intravenously injected 5 mL of cigarette soakage solution, containing approximately 5.7 mg nicotine, in a suicidal attempt. She survived and recovered completely in nearly 24 h.¹³

Three cases of fatal multidrug poisoning with nicotine and other agents have been described so far, to the best of our knowledge.¹⁴⁻¹⁶ Among these, a single case of fatal multidrug poisoning involving nicotine has been described in a 46-year-old man who was found dead in his bed after attaching 25 transdermal nicotine patches to his thorax and abdomen and drinking two bottles containing tobacco, nicotine and other drugs such as tramadol and diphenhydramine.¹⁶ Since both nicotine and tramadol have the potential to cause severe central nervous system depression accompanied by cardiovascular abnormalities and sudden respiratory failure, this case is the only one previously reported showing some analogies with ours, the only difference being the opioid drug (*i.e.* methadone *vs* tramadol).

Recently, three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes have been described, two of whom occurring in the same woman. All the cases have been successfully treated with activated charcoal.¹⁷

Nicotine has also been reported as a potential chemical weapon, since it is highly toxic, it can be purchased without restriction, and there is no restriction for airline passengers. The Norwegian fanatic extremist and terrorist Anders Behring Breivik, before killing 77 people, published on-line a *relatively simple process to convert hollow projectiles into chemical weapons, by injecting them with a biological or chemical toxin...* and, after careful consideration of alternatives, including heroin, various insecticides and cyanide, he concluded that the ideal is nicotine.¹⁸

Conclusions

E-cigarette is a misleading term used to identify an aerosolizing delivery device equipped with a disposable cartridge which

contains nicotine in solution, usually diluted with propylene glycol. Despite being marketed as cigarettes, these devices resemble multi-dose inhalers, nebulizers, or other devices loaded with a drug (*i.e.* albuterol, used for asthma treatment).¹⁹ As such, on April 25, 2011, the US Food and Drug Administration announced the aim of regulating e-cigarettes as tobacco products, having failed in its initial attempt to regulate them as drug-delivery devices.²⁰ To the best of our knowledge, this case is the very first describing multidrug poisoning with nicotine and methadone, due to both ingestion and *i.v.* injection of the content of an e-cigarette refill, incorrectly mixed with methadone, that was bottled in a generic vial. The patient had a favourable outcome, mainly attributable to the relatively small dose of nicotine assumed. Moreover, we did not observe any sign or symptom of methadone intoxication, probably due to the chronic addiction of the patient. It should be considered, however, that the small volumes of the refill's content makes it easy to ingest or inject higher and potentially lethal doses and thereby poses serious threats for the future.²¹ E-cigarettes and refill solutions can be easily purchased, also on the Web through virtual stores that are poorly regulated. This should raise additional concerns about the increasing use of e-cigarettes, that may hence be considered a new and easily available form of accidental or intentional poisoning as uncontrolled forms of delivery of high-dose nicotine or other potentially toxic compounds. Emergency physicians should hence clearly acknowledge the ingestion and injection of the content of e-cigarette refills as a new and potential form of acute poisoning.

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