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Case report

Death due to ingestion of nicotine-containing solution: Case report and review of the literature

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ABSTRACT

Nicotine, a lipid-soluble alkaloid obtained from the dried leaves of *Nicotiana*, is most frequently encountered in tobacco products for smoking, chewing or sniffing as well as in a limited number of pesticides. Though nicotine is one of the most toxic drugs of abuse, it has rarely led to fatalities. Sudden death can be caused by cardiovascular arrest, respiratory muscle paralysis and/or central respiratory failure. A 42-year-old man was found dead by his wife. He was lying on the floor, next to a box containing many empty bottles of beer and vodka. Some labeled chemical bottles found at the scene contained various substances, including nicotine and brucine. Gross examination of the organs at autopsy revealed no specific findings. The toxicological examination failed to disclose any lethal toxic agents other than a high concentration of nicotine and its primary metabolite cotinine in femoral venous blood (2.2 μg/mL). Blood alcohol was determined to be 2.1 g/L in femoral venous blood. Only a paucity of fatal cases of nicotine poisoning has been reported in the literature so far.

1. Introduction

Nicotine is a natural highly lipid-soluble alkaloid obtained from the dried leaves and stems of *Nicotiana tabacum* and *Nicotiana rustica*, where it is present in concentrations of 0.5–8% [1]. Nicotine is an addictive drug used in cigarettes as well as in sniffing and chewing tobacco. Gums and patches used during withdrawal of smoking also contain nicotine and the substance is also sold commercially as pesticide. In humans, nicotine is extensively transformed with oxidation to cotinine as its main metabolite in the liver. Cotinine has approximately 10 times the half-life of nicotine (20 h) and is therefore a more stable marker of exposure over time than nicotine (average half-life 2–3 h) [2]. During cigarette smoking nicotine, nicotine is absorbed through the oropharyngeal mucosa and then passes into the lungs where it is rapidly absorbed into the pulmonary circulation. It then enters the arterial circulation and quickly moves to the brain. Nicotine readily diffuses into tissue, where it binds to nicotinic cholinergic receptors [3].

Two issues are particularly relevant in understanding the pharmacodynamics of nicotine. First, the nicotine dose–response relationship is complex. Low doses may stimulate neural systems, whereas higher doses depress them. For example, low doses of nicotine induce central or peripheral nervous system stimulation with arousal and an increase in heart rate or blood pressure. At high (intoxicating) doses, nicotine causes ganglionic blockade resulting in bradycardia, hypotension, and depressed mental status [4]. Thus, nicotine is one of the most toxic of all poisons known and has a rapid onset of symptoms. Apart from producing a burning sensation in the mouth and throat, it may cause sudden respiratory failure by acting on the peripheral and central nervous systems; death may also be caused by respiratory muscle paralysis and/or for cardiovascular collapse [5–8]. Despite its high toxicity, nicotine rarely results in serious or fatal poisoning [8–18].

Here, we report the case of a man who was found dead at his home. Toxicological analyses revealed fatal ingestion of a concentrated-nicotine solution.

2. Case report

A 42-year-old man was found lying dead on the floor in his garage, next to a box containing many empty bottles of beer and vodka. He was found by his wife, who had not seen him for many hours. Some small bottles discovered at the scene contained various substances (brucine, nicotine, zinc dust, indium, arsenic,

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Fig. 1. Bottle found at the death scene, labeled "Nicotine, pure".

Teflon dust, phosphoric acid); the glass bottle labeled "nicotine, pure" was half filled with a clear brown liquid (Fig. 1) which had a strong, pungent odor.

A medico-legal autopsy was performed. The man was 184 cm tall and weighed 84 kg. External examination of the body was essentially negative regarding the cause of death. There were no signs of external injuries or violence preceding death.

At autopsy, the brain weighed 1500 g, had a stiff consistency and showed edema and slight vascular congestion. The lungs were heavily edematous and congested and weighed 900 g (left) and 880 g (right). The heart weighed 500 g and contained a moderate volume of liquid blood; the valves and coronary arteries were regular with no signs of arteriosclerosis. The stomach contained 110 g of a brownish-yellow liquid with a strong, pungent odor. The urinary bladder contained 40 mL of urine. The abdominal organs were congested.

Femoral venous blood, gastric contents and urine were collected for toxicological analyses. Moreover, samples from the chemical bottles were separately submitted for analysis.

3. Toxicological analysis

For the systematic toxicological analysis, urine samples and stomach contents were basified by standard procedures and the extracts were analyzed using gas chromatography/mass spectrometry (GC–MS) [19–21].

Nicotine and cotinine were quantitatively analyzed by GC–MS, using nicotine D_4 as internal standard. Nicotine, cotinine and nicotine D_4 were purchased from LGC-Promochem (Wesel, Germany). All buffer substances and solvents were obtained from Merck (Darmstadt, Germany).

Brucine was quantitatively analyzed in femoral venous blood by protein precipitation with acetonitrile as well as by high-performance liquid chromatography (RP-HPLC) using a Purospher RP-18 micro-column with a flow rate of 1.2 mL in the system acetonitrile/phosphoric acid (0.072%) obtained from Merck (Darmstadt, Germany) [22].

Table 1
Results of toxicological analysis.

	Femoral venous blood	Stomach	Urine
Nicotine	2.2 μg/mL	1000 mg	Nicotine + alkaloid
Cotinine	2.2 μg/mL		
Alcohol	2.1 g/L	–	2.4 g/L
Brucine	Not detectable[a]	70 mg	Brucine + alkaloid
Others			Caffeine

[a] Limit of detection: 0.05 μg/mL.

GC–MS confirmed the presence of nicotine and brucine in the stomach contents and also detected nicotine, brucine and caffeine in urine. GC–MS quantitative analysis revealed nicotine and cotinine concentrations 2.2 μg/mL in femoral venous blood. GC–MS revealed that the glass bottle labeled "nicotine, pure" found at the death scene contained undiluted, pure nicotine. Brucine was not detectable in femoral venous blood (limit of detection: 0.05 μg/mL) but the absolute amount of brucine was 70 mg in stomach content (Table 1). Nicotine quantity in the stomach was 1000 mg.

Ethanol was determined in femoral venous blood and urine by Head-Space-Gaschromatography. The blood alcohol concentration was 2.1 g/L.

4. Discussion

Nicotine is a naturally occurring water-soluble alkaloid which is considered to be a major factor in sustaining tobacco addiction. Cigarettes contain 8–20 mg of nicotine (depending on the brand), but smokers actually absorb only about 1 mg per cigarette. Many brands of cigars contain at least 10–20 times that amount, and some may even contain 50 times more nicotine than cigarettes [23]. The average dose is 3.6 mg for snuff and 4.5 mg for chewing tobacco; transdermal nicotine patches come in several dosages (7–21 mg/24 h) [24].

Although the active, circulating compound is the same stimulant in all cases, the bioavailability of nicotine may differ in tobacco leaf and various other preparations [16].

Nicotine acts on the parasympathetic and sympathetic nervous system, where it binds to acetylcholine receptors. In general, the central nervous system is stimulated by small doses of nicotine but depresses by large doses [25,26].

The estimated lethal dose of nicotine in adults ranges from 0.5 to 1.0 mg/kg of body weight, corresponding to a total dose of 30–60 mg [27]. Toxic symptoms might be seen at doses as low as 2–5 mg. However, individuals vary widely in their tolerance to the toxic effects of nicotine [6].

Non-fatal cases of intentional or unintentional nicotine intoxication have been reported in the literature [6,28–33]. In such cases, nicotine stimulates autonomic ganglia and induces the classical effects of cholinergic excess, such as muscle fasciculations and muscarinic symptoms (nausea, vomiting, increased salivation, dizziness, headache, and vision or hearing changes). Massive nicotine ingestion frequently causes dangerous medical complications such as seizures, central nervous system changes, cardiovascular effects and respiratory failure [34–36]. Victims who are not hospitalized immediately may face rapid progression to hypotension and death. The most common mechanisms of death from nicotine intoxication are respiratory failure due to peripheral neuromuscular blockade and cardiovascular arrest [5,7,16].

Though nicotine is one of the most toxic drugs of abuse, it rarely leads to fatalities. Fatal poisoning from concentrated-nicotine solution and pesticides have occurred in the past [8–17,37,38], and

Table 2
"Blood" (not specified whether heart or femoral) concentration reported in fatal cases of nicotine poisoning.

	Nicotine	Cotinine	Note
Levoie et al. [16]	13.6 μg/mL blood	/	Sample taken before death Autopsy not performed
Sanchez et al. [8]	3.7 μg/mL (a) 1.2 μg/mL (b) blood	/	Sample taken 11 (a) and 57 h after death (b) Autopsy not performed
Takayasu et al. [17]	6.3 μg/mL blood	/	–
Our case	2.2 μg/mL peripheral blood	2.2 μg/mL peripheral blood	

nicotine has been reported to cause death in two cases [18,39]. However, only a few cases of fatal nicotine poisoning have been reported during the last 20 years [8,16,17].

In the present case, GC–MS analysis revealed nicotine and cotinine concentrations of 2.2 μg/mL in femoral venous blood. The toxicological investigations did not disclose any other lethal toxic agents. However, the elevated alcohol concentration in femoral venous blood (2.1 g/L) may have contributed to fatal outcome. The presence of nicotine and its alkaloid in the stomach confirmed the oral ingestion of these toxic agents and correlated with the half-filled bottle of nicotine discovered next to the body. It was therefore assumed that the nicotine volume missing from the bottle was enough to induce a lethal outcome in the man after oral ingestion. With regard to the role of brucine, we observed a discrepancy between its value in the stomach (70 mg) compared with that we found in the femoral venous blood (non-detectable). Hence, we hypothesized death occurred for lethal ingestion of nicotine and alcohol, shortly after the victim started swallowing brucine. The pathological findings at autopsy, including congested and edematous lungs and brain and a hypertrophied heart, were consistent with death from cardiorespiratory failure secondary to drug poisoning.

Lavoie and Harris [16] reported a serum nicotine concentration of 13.6 μg/mL as determined at the hospital where a patient was admitted after intentional ingestion of nicotine-containing solution. Takayasu [17] reported a postmortem blood concentration of 6.3 μg/mL in a 44-year-old woman who committed suicide by oral self-administration of nicotine solution. A 32-year-old man, who died after applying transdermal nicotine patches, had a blood nicotine concentration ranging from 3.7 μg/mL (11 h after death) to 1.2 μg/mL (57 h after death) [8].

It must be emphasized that in the cases previously published, an autopsy was not performed in all cases and that these cases lack uniformity in the blood examined (heart vs. femoral venous) and the postmortem sampling interval failed to include a cotinine evaluation (Table 2). It is well known that blood specimens obtained from the heart can be influenced by the agonal flow towards the large vessels and the redistribution of basic lipophilic molecules from the lung parenchyma and stomach [18]. For this reason, the analysis of peripheral blood is often to enable a definitive interpretation of postmortem toxicological analyses [40].

Thus the femoral venous blood concentration measured in the present case is much higher than the mean value reported in literature and can be regarded as an indicator of fatal nicotine poisoning [27]. In addition, comparison with previously reported non-fatal cases of nicotine poisoning shows that the blood nicotine concentration of 2.2 μg/mL detected here was about 30 times higher than the usual level at which people, usually start showing neurological symptoms of nicotine poisoning [34].

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