E-cigs: toxic threat to dogs

Author : LOTFI EL BAHRI

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Both tobacco and nicotine replacement therapies are a source of acute poisoning in humans and animals. A new source of nicotine exposure – electronic cigarettes (e-cigs) – is also a potential source of poisoning in both humans and dogs[1].

Serious or fatal cases of poisoning of puppies after ingestion of an owner's e-cig have been reported[2,3,4]. E-cigs, or electronic nicotine delivery systems, are in "a category of consumer products designed to deliver nicotine to the lungs after one end of a plastic or metal cylinder is placed in the mouth, like a cigarette or cigar, and inhaled to draw a mixture of air and vapours from the device into the respiratory system"[5]. Usage of e-cigs has exponentially increased during the past few years[6].

In humans, reports to US poison control centres of possible nicotine toxicity tripled from 2012 to 2013[7]. In the UK, a 300 per cent increase in e-cigs poisoning in the past 12 months was recorded by the Veterinary Poisons Information Service (VPIS)[8]. Veterinarians should be aware e-cigs have the potential to cause significant toxicity in pets.

An e-cig has four parts: the cartridge with a nicotine-containing solution (e-liquid) in a variety of flavours and diverse chemical additives (propylene glycol as humectant, glycerine); the electronic vaporisation system (atomiser chamber and heating coil); battery; and light-emitting diode to reproduce the appearance of a burning cigarette tip[1,9]. The "flavoured juice" of e-liquid produces an odour that attracts pets. E-cig poisoning may occur by the animal swallowing the nicotine cartridge, after putting a tooth through the packaging biting into an e-cig refill, or by absorbing it through the mucous membranes or the skin[2,3,4]. Nicotine poisoning is a veterinary emergency.

Toxicokinetics

Nicotine, a weak base alkaloid (pKa = 8.5), is poorly absorbed from the stomach because it is ionised in the acidic gastric fluid, but is well absorbed in the small intestine, which has an alkaline

pH and a large surface area[10],[11]. E-liquids have an alkaline pH (7.5 to 8.5), which enhances intestinal absorption[12].

Nicotine is lipid soluble and well absorbed through skin and mucous membranes[13]. Oral bioavailability is about 30 per cent to 40 per cent because of the high hepatic first-pass metabolism[14]. The binding plasma proteins are less than five per cent, allowing for rapid diffusion in the tissues[15]. Nicotine easily crosses the blood-brain barrier. The steady-state volume of distribution averages 2.6L/kg[11]. In humans, about 70 per cent to 80 per cent of nicotine is metabolised rapidly in the liver to cotinine and 3'- hydroxycotinine[16]. The terminal half-life average is 11 hours[17]. About 16 hours after ingestion, nicotine is completely excreted through the kidneys[18].

Risk assessment

Exposure to e-cigs may be dangerous because they can be highly concentrated in nicotine with the amount in the cartridge reaching 24mg (full flavour)[9].

A major danger seems to be refill containers that often come in 30ml bottles and can contain up to 24mg/ml nicotine or even higher[19],[20]. Some refill solutions can be bought on the internet with concentrations as 100mg/ml. In dogs, 10mg/kg orally is potentially fatal[21]. The oral LD50 of nicotine in dogs is 9.2mg/kg[22]. VPIS suggests 1mg/kg of ingested nicotine is potentially toxic[2]. Toxicosis appear more common in young animals[18].

Toxic mechanism

Nicotine binds stereoselectively to nicotinic acetylcholine receptors (nAchRs), which are pentameric ligand-gated ion channels (LGICs), localised in the peripheral and central nervous system, autonomic ganglia, sympathetic and parasympathetic nervous system, and skeletal neuromuscular junctions[10],[23].

LGICs are a group of transmembrane ion channel proteins that open to allow ions such as Na+, K+, Ca2+ or C- to pass through the membrane in response to the binding of a neurotransmitter. The nAchRs are a complex of five subunits. In the mammalian brain, there are as many as nine ? subunits (?2 to ?10) and three ? subunits (?2 to ?4)[24].

The function of such receptors located at synapses is to convert the chemical signal of presynaptically released neurotransmitter directly and very quickly into a postsynaptic electrical signal[23]. Stimulation of central nAchRs by nicotine results in the release of a variety of neurotransmitters in the brain, essentially dopamine and norepinephrine[24].

Nicotine also activates the hormonal pathway and stimulates the release of antidiuretic hormone from the posterior pituitary resulting in hyponatraemia[25],[26].

E-cigs usually use a lithium ion battery disc/button of three volts. This can allow an electric current to pass to the tissues of the gastrointestinal tract in case of ingestion, resulting in a current-induced severe necrosis with tissue damage and even perforation of the oropharynx, oesophagus, stomach or small intestine[27]. These lesions occur with only 15 to 30 minutes of contact[27].

Clinical features

Nicotine poisoning has a rapid onset of clinical signs, generally within 15 minutes to an hour of ingestion to the e-liquid[2,4,18,28]. Delayed onset and prolonged symptoms may be seen with cutaneous exposure. Hyperstimulation of nAchRs produces a constellation of effects.

- **Gastrointestinal:** hypersalivation, vomiting, diarrhoea and abdominal pain.
- **Cardiovascular:** hypertension, cardiac arrhythmia and collapse.
- **Central nervous system:** ataxia, weakness, mydriasis, tremors, seizures and coma.
- **Pulmonary:** initial tachypnoea, followed by respiratory depression.

Laboratory results indicate hypokalaemia[25,29]. Death is due to respiratory muscle paralysis. Postmortem findings revealed no specific lesions[18,30]. A case of intracerebral haemorrhage associated with ingestion of tobacco snuff has been reported[31].

Diagnosis

Diagnosis of nicotine intoxication is suggested by a history of exposure and rapid onset of clinical signs. Differential diagnoses include intoxication with organophosphate or carbamate insecticides, strychnine, metaldehyde, bromethalin, methylxanthines, mycotoxicosis (Penitrem A, Roquefortine), and muscarinic mushroom group (*Clitocybe* and *Inocybe* species).

Toxicological diagnosis is based on analysis of vomitus, gastric contents, blood and urine by thin-layer chromatography, gas chromatography/mass spectrometry or high performance liquid chromatography[18,32,33]. In an intoxicated dog, nicotine serum concentration was 200ng/ml[18].

Management

There is no antidote for nicotine poisoning. In case of ocular exposure, the eyes should be copiously irrigated with physiologic saline for at least 20 minutes. The mouth may be rinsed with water. Bathe with copious soap and rinse in case of skin contamination. Staff should wear appropriate skin-protective gear. If e-liquid is spilled on clothing, the clothing should be removed. Management of e-cigs poisoning is listed in Table 1 [34,35].

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Treatments to avoid	Induced emesis is not recommended (risk of rapid-onset of seizures).
	Activated charcoal per os is contraindicated in a patient that is convulsing or in coma.
	H_2-blocking agents or proton pump inhibitors are contraindicated (absorption of nicotine is enhanced in an alkaline medium).
Treatments to administer	Attention to airway, breathing and circulation is paramount.
	Oxygen may be needed to treat respiratory distress.
	Antiemetics may be required (maropitant citrate injectable).
	Activated charcoal (2g/kg to 5g/kg) mixed with water to make a slurry via nasogastric tube, after the airway is secured.
	Treat seizures: – diazepam IV bolus (0.5mg/kg to 2mg/kg). Repeat if necessary within 20 minutes (serum half-life in dogs: 2.5 to 3.2 hours) up to three times in a 24-hour period – or lorazepam, a long-acting benzodiazepine, IV bolus (0.2mg/kg).
	Cardiac rhythm and blood pressure should be monitored.
	IV fluids to correct dehydration and electrolyte abnormalities.
	Prompt removal of the battery from the gastrointestinal tract by endoscopy or surgery.
	Sucralfate (0.5g to 1.0g per os, two to four times a day) to help heal the gastrointestinal tract, for five to seven days.

Table 1. Treatments to avoid and to administer

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