CHEST

Severe Acute Toxicity of Inhaled Nicotine and e-Cigarettes

Seizures and Cardiac Arrhythmia

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A recent statement from the US Food and Drug Administration (FDA)[1] expresses concern regarding a potential safety issue related to seizures reported following e-cigarette use, particularly in youth and young adults. Since the publication of this statement in April 2019, the FDA announced an update on August 7, 2019, stating that the FDA continues to receive more reports of seizure cases (total 127) following e-cigarette use. This number is probably an underestimation due to the voluntary nature of the reports.[2]

Severe acute toxicity and fatal accidents of human intake of nicotine have been known for decades. Seizures due to nicotine poisoning have been reported in intentional or accidental swallowing of nicotine-containing e-liquid.[3,4] The median lethal dose for nicotine is 0.5 to 1 mg/kg body weight in adults.[5] Animal studies show that the median lethal dose for nicotine is 70 mg/kg (oral administration)[6] and 23.5 mg/kg (intraperitoneal injection)[7] in rats. However, the cases of seizures discussed by the FDA are with ordinary inhalation use of e-cigarettes.

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Acute Toxicity of Inhaled Nicotine

Unlike oral or intraperitoneal routes of administration, in which only 30% nicotine gets into the systemic circulation due to first-pass metabolism, inhaled aerosolized nicotine is quickly absorbed into the pulmonary circulation and the heart, then into the coronary and systemic circulations, and the brain. With the same dose of delivery, nicotine aerosol and e-cigarette smoke through the inhalation route not only have higher bioavailability and higher plasma concentrations but also lead to a substantially faster rising phase in the pharmacokinetic parameters in the arterial blood.[8] Nicotine acts on nicotinic acetylcholine receptors (nAChRs) in the nervous systems and other organ systems, resulting in a variety of health effects. Some subtypes of nAChRs desensitize quickly. Therefore, the rapidity of the increase in plasma nicotine concentrations greatly impacts systemic functions such as respiration, circulation, and hemodynamic variables, as well as seizures. We reported previously that inhaled nicotine induces cardiovascular (continuously recorded arterial BP) responses within 3.2 $\pm$ 0.9 s from the start of aerosol inhalation.[9]

Inhalation toxicity is formally reported as the median lethal concentration (LC50) and its CI, as well as exposure duration, as recommended by the Organization for Economic Co-operation and Development guidance document on acute inhalation toxicity testing.[10] We established the LC50 of inhaled nicotine as 2.3 mg/L in air (20 min) with a CI of 1.46 to 4.96 mg/L in rats. We reported severe acute toxic signs, including seizures and respiratory depression (eg, hypopnea, apnea interspersed with gasps) following inhalation exposure of high-dose nicotine aerosol in the animal model.[8] In addition, our studies showed that inhaled nicotine impairs cardiovascular system function and hemodynamic variables, including irregular fluctuations of BP and organ blood flow, as well as arrhythmias such as bradycardia, irregular rhythm, sinoatrial block, sinus arrest, second- and third-degree atrioventricular block, and supraventricular escape rhythm, when the nicotine levels and pharmacokinetics are similar to those of a human smoking a cigarette. These effects can be blocked by the nAChR antagonist mecamylamine.[9]

Alpha-7 (α7) nAChRs are highly expressed in the amygdala, an area involved in seizure generation and epileptogenesis. Nicotine (intraperitoneal injection) elicits convulsive seizures by activating amygdala neurons, mainly via α7 nAChRs in mice and rats.[11] Activation of nAChRs by nicotine stimulates glutamate release mediated through calcium-calmodulin cascades. Glutamate activates NMDA receptors leading to seizures.[12]

Respiratory neurons in the pre-Bötzinger complex, a medullary microcircuit at the core of the breathing central pattern generator that produces the rhythm of inspiration in mammals,[13] expresses functional α4* nAChRs, which mediate cholinergic regulation of respiration.[14] nAChRs are also present in respiratory motor neurons in the ventral horn of the spinal cord (including the phrenic nucleus) that innervate respiratory muscles and medullary cranial motor nuclei such as the hypoglossal nucleus that regulate airway resistance. Excessive stimulation of nAChRs leads to disturbance of respiratory rhythm and patterns.

Endogenous acetylcholine (ACh) or exogenous nicotine activates presynaptic and postsynaptic nAChRs that facilitate glutamatergic neurotransmission to and depolarize parasympathetic preganglionic cardiac vagal neurons in the nucleus ambiguus[15]; the postsynaptic effects are mediated by α3β2/α6βX and α3β4 nAChRs.[16] nAChRs mediate ganglionic transmission in the peripheral (sympathetic and parasympathetic) autonomic nervous systems in mammals. Specifically, ACh activates α3β2 and α7 nAChRs on the postganglionic parasympathetic neurons that innervate the heart.[17] Inhaled nicotine stimulates these nAChRs, leading to dysfunction of autonomic nervous system regulation of cardiovascular function; this action results in the bradycardia, arrhythmia, and fluctuation of arterial BP observed in acute nicotine intoxication.

The intoxication signs we observed in animals during acute nicotine aerosol inhalation[8] are consistent with those of nicotine poisoning by e-liquid ingestion observed in patients.[3,4] Our studies show a link between inhaled nicotine and seizures as well as other life-threatening conditions such as respiratory depression and arrhythmia.

Clinical Relevance and Recommendations

Seizures are caused by abnormal electrical activity within the brain, leading to falls, loss of consciousness, airway obstruction, hypoventilation, hypoxemia, coma, and death. If persistent or prolonged, these seizures can potentially cause brain damage, especially in youths whose CNS are not fully developed, leading to permanent pathological changes.

When convulsive seizures occur, the patient should be placed in the lateral decubitus position to avoid aspiration. It is also important to note the duration and type of seizure activity. In general, the diagnostic evaluation of seizures consists of a medical history, physical and neurological examination, laboratory tests, EEG, and CT scan, and/or MRI. Possible causes include infection, toxic-metabolic derangements, structural abnormalities such as tumor or hemorrhage, genetics, or idiopathic. History of e-cigarette or other tobacco product use should also be included in the differential diagnosis for new-onset seizures in teenagers and young adults as either the direct cause or indirectly triggered by their underlying medical conditions. Blood levels of nicotine and/or cotinine should be included in the laboratory testing. In addition to early removal of nicotine and supportive measures, antiepileptic medication should be considered if seizures persist or recur.[3]

The danger of cardiac arrhythmia caused by acute nicotine toxicity depends on the type of arrhythmia and whether it results in significant hemodynamic disturbance. Among other symptoms (eg, anxiety, seizures, increased bronchial secretion, salivation), those of parasympathetic stimulation such as bradycardia, hypotension, lethargy, and cardiac arrest can lead to poor outcomes.[3] The cardiovascular and respiratory symptoms caused by parasympathetic stimulation such as changes in respiratory rate and pattern, oxygen saturation, arterial blood gas, BP, and ECG should be closely monitored. Aggressive respiratory support should be provided.[5] Atropine should be given for bradycardia or dyspnea due to pulmonary secretions. If hypotension and arrhythmia continue, vasopressors or antiarrhythmic medications should be considered.

Anesthetics used for general anesthesia are potentially epileptogenic, including volatile agents such as sevoflurane, isoflurane, and enflurane, IV agents such as etomidate, and, to a lesser extent, propofol, in patients with or without a history of epilepsy.[18,19] These agents can also induce arrhythmia and hemodynamic dysfunction intraoperatively. With the new FDA warning and collective reports related to nicotine toxicity, it is prudent to include information regarding e-cigarette use in the preoperative evaluation. Intraoperatively, if not avoidable, sevoflurane concentrations should be controlled with < 1.5 minimal alveolar concentrations, or combined with narcotics,

propofol, or nitrous oxide to lower the requirement of sevoflurane. Vigilance in monitoring and treating seizures and arrhythmia associated with e-cigarette use during surgery, especially in teenagers and young adults, is important to prevent perioperative morbidity and mortality.

With the alarming increase in e-cigarette use worldwide, especially among youth and young adults, it is time for medical professionals to recognize the emerging problems, to educate the public about the dangers of e-cigarettes, and to develop strategies for the prevention and treatment of e-cigarette-associated acute intoxication and chronic diseases.

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