VITAMIN E ACETATE – A POTENTIAL FACTOR IN E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY (EVALI)

Octan witaminy E jako potencjalny czynnik wywołujący ostre uszkodzenie płuc związane z używaniem e-papierosów (EVALI)

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Abstract

E-cigarettes are gaining popularity as an alternative to traditional cigarettes, especially among young people. However, their use is associated with severe health consequences, such as e-cigarette or vaping product use-associated lung injury (EVALI), a lung injury linked to e-cigarette use or vaping. The objective of this study was to discuss the health consequences of using e-cigarettes, with particular emphasis on the negative effects of vitamin E acetate. Google Scholar, PubMed and SpringerLink databases were used for the literature review. The search terms in English included: „EVALI," „lung injury," „pulmonary," „respiratory," „e-cigarette," „vitamin E acetate," „vaping," and „vape." Articles published from 2019 onwards were included. Recent studies focus on the role of vitamin E acetate in the pathophysiology of EVALI. The mechanism by which this substance can cause lung injury remains unknown, but its potential harmfulness may result from its decomposition during heating into toxic substances such as formaldehyde, acetaldehyde, acrolein, and ketenes. Tocopherol acetate, as a surface-active substance, damages the pulmonary surfactant, leading to acute respiratory failure. Despite the increasing popularity of e-cigarettes, their negative health effects are still poorly described. In particular, determining long-term consequences is challenging due to the short observation period for e-cigarette users. EVALI is diagnosed based on the exclusion of other conditions and a positive history of e-cigarette use.

Streszczenie

E-papierosy zyskują na popularności jako alternatywa dla tradycyjnych papierosów, szczególnie wśród młodych ludzi. Jednakże ich używanie wiąże się z poważnymi konsekwencjami zdrowotnymi, takimi jak uszkodzenie płuc związane z używaniem e-papierosów lub tzw. wapowaniem (EVALI). Celem niniejszej pracy jest omówienie konsekwencji zdrowotnych wynikających z korzystania z e-papierosów, ze szczególnym uwzględnieniem negatywnych skutków działania octanu witaminy E. Przeglądu piśmiennictwa dokonano z wykorzystaniem bazy Google Scholar, PubMed oraz SpringerLink. Wyszukiwane frazy w języku angielskim: „EVALI", „lung injury", „pulmonary", „respiratory", „e-cigarette", „vitamin E acetate", „vaping" oraz „vape". Włączono artykuły opublikowane od 2019 roku. Najnowsze badania koncentrują się na roli octanu witaminy E w patofizjologii EVALI. Mechanizm, w którym substancja ta może wywołać uszkodzenie płuc, pozostaje nieznany, ale potencjalna szkodliwość tego związku chemicznego może wynikać z jego rozkładu podczas podgrzewania do toksycznych substancji, takich jak formaldehyd, aldehyd octowy, akroleina oraz keteny. Octan tokoferolu jako substancja powierzchniowo czynna uszkadza surfaktant, co prowadzi do ostrej niewydolności oddechowej. Pomimo rosnącej popularności e-papierosów, negatywne skutki zdrowotne są nadal niewystarczająco opisane. W szczególności trudność sprawia określenie długofalowych konsekwencji z powodu krótkiego czasu obserwacji osób korzystających z e-papierosów. EVALI jest rozpoznaniem stawianym po wykluczeniu innych schorzeń oraz na podstawie dodatniego wywiadu w kierunku stosowania e-papierosów.

Keywords: youth; pneumonia; nicotine; vaping; e-cigarette

Słowa kluczowe: młodzież; zapalenie płuc; nikotyna; wapowanie; e-papieros

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Introduction and aim

With the growing popularity of e-cigarettes, the incidence of acute respiratory failure due to interstitial pneumonia has increased among their users. In 2019, the United States saw a sharp rise in such cases, primarily among young individuals without comorbidities. This prompted researchers to investigate the etiopathogenesis, identifying vitamin E acetate, an ingredient in some e-cigarette liquids, as a potential contributing factor.

The aim of this study is to describe e-cigarette or vaping product use-associated lung injury (EVALI) and to identify potential risk factors. Special attention should be paid to vitamin E acetate, as it is considered a key trigger of pneumonia among e-cigarette users and individuals exposed to passive vaping.

Review methods

The literature review was conducted using the PubMed, Google Scholar, and SpringerLink databases. Only papers published in English since 2019 were considered. In order to obtain precise results, the following English-language search terms were used: „EVALI", *„lung injury"*, *„pulmonary"*, *„respiratory" „e-cigarette"*, *„vitamin E acetate"*, *„vaping"* and *„vape"*. The literature review was expanded to include data obtained from the websites of the Ministry of Health and the Institute of Economic Forecasts and Analysis. A total of 95 publications were identified. After excluding duplicates and incomplete, irrelevant, unreliable, or methodologically inadequate works, as well as those containing outdated medical data, 28 scientific publications were ultimately included in the review.

The state of knowledge

Definition and epidemiology of EVALI

EVALI is an acute lung injury resulting from the inhalation of substances heated by e-cigarettes or other devices. In August 2019, the United States reported a sharp rise in hospital admissions for acute respiratory distress syndrome of unknown origin, primarily among young people without chronic illnesses [1]. This has been linked to the use of e-cigarettes, with 2,807 documented cases and 68 deaths. Several similar clinical cases had been reported in the United States before 2019. The number of cases rose so rapidly in 2019 that it met the criteria for an epidemic in the United States.

In the early stage of identifying the etiological factor, vitamin E acetate (tocopherol acetate) was considered, as it was used as a thickening agent in e-liquids, particularly those enriched with tetrahydrocannabinol (THC) [3]. Although vitamin E acetate is widely used in the food and cosmetics industries, its presence in e-cigarette aerosol likely contributed to the development of EVALI [4, 5].

Composition of e-cigarette liquids

The composition of e-cigarette liquids remains controversial, with nicotine concentrations ranging from 15 to 50 mg/mL. In their study on the negative effects of e-cigarette use, Bhave and Chadi reported the actual nicotine content in these liquids. Assuming a liquid volume of 2 mL and a nicotine concentration of 5%, the total nicotine content can reach 100 mg [6]. This amount of liquid is typically inhaled within about 1 hour. The intake of such a high dose of nicotine over a short period is toxic [7]. In addition to nicotine and water, e-liquids also contain multiple toxic and carcinogenic chemicals, heavy metals, and contaminants. These substances include propylene glycol, acetaldehyde, formaldehyde, tobacco alkaloids, nitrosamines, free radicals, polycyclic aromatic hydrocarbons, benzene, phthalates, caffeine, volatile organic compounds, acrolein, isoprene, nickel, phenol, chrysene, cadmium, toluene, butanone, and various flavouring compounds [8].

Diagnosis of EVALI

EVALI is often diagnosed by exclusion, as its nonspecific symptoms resemble those of infection. A thorough medical history is essential, including respiratory symptoms (such as dyspnoea, cough, chest pain, respiratory distress, and hypoxia), other systemic symptoms, and a history of e-cigarette use within the past 90 days [1, 8]. Physical examination often shows fever or low-grade fever, tachycardia, tachypnoea, and hypoxemia, with clinical severity ranging from mild illness to the need for intubation and mechanical ventilation [8]. A chest X-ray should be performed in patients with suspected EVALI. If the X-ray is abnormal or inconclusive, non-contrast computed tomography (CT) is recommended. CT angiography may also be considered as an alternative. EVALI can occur in many forms of lung damage, such as organizing pneumonia, acute eosinophilic pneumonia, diffuse alveolar damage, and lipoid pneumonia [9]. Organizing pneumonia, which presents radiographically as bilateral, patchy ground-glass opacities with peripheral and perilobular

consolidations, is the most common type. An inverted halo sign, also known as the "atoll sign" because of its resemblance to a coral atoll, is a hallmark of organizing pneumonia [10, 11]. The inverted halo sign is a distinctive radiological CT finding, defined by a dense ring of complete opacification surrounding a central area of ground-glass opacity [11].

Diffuse alveolar damage, which appears on chest X-ray and CT as volume loss, predominantly lower-lobe consolidations, and ground-glass opacities, is yet another most common type of lung injury. Radiological findings of organizing pneumonia and diffuse alveolar damage may overlap, with both showing interlobular septal thickening and the cobblestone sign [9]. Imaging plays a crucial role in the early diagnosis of EVALI and treatment initiation.

The role of vitamin E acetate in the pathophysiology of EVALI

Vitamin E acetate is a synthetic ester of tocopherol and acetic acid, added in e-cigarette liquids as a thickening agent [12, 13]. It is a common and well-studied ingredient in cosmetics and dietary supplements, exhibiting antioxidant effects when administered orally or applied topically to the skin [13]. However, data on the safety of its inhaled form (via e-cigarettes) is still limited, with studies suggesting that vitamin E acetate plays an important role in the pathophysiology of EVALI.

Blount et al. collected bronchoalveolar lavage fluid (BALF) from patients hospitalized for EVALI and from healthy individuals (controls). Vitamin E acetate was detected in 94% of samples from EVALI patients and none of the control samples [12]. EVALI patients had elevated BALF tocopherol acetate, with a median value of 21.9 ng/mL [14]. Duffy et al. found that tocopherol acetate was present in 60.5% of e-cigarette liquids used by EVALI patients [4].

The mechanism by which vitamin E acetate causes EVALI remains unknown and is still under investigation. The harmful effects of this compound may arise from its loss of chemical stability when heated, leading to decomposition into toxic substances such as formaldehyde, acetaldehyde, acrolein, and ketenes [15, 16]. Ketenes are unsaturated ketones that cause cytotoxic damage to the pulmonary alveoli and surrounding capillaries. They are considered a potential contributor to chemical pneumonia in EVALI [16]. Animal studies suggest a possible pathophysiological mechanism by which vitamin E acetate causes lung damage. Vitamin E acetate–exposed mice were found to have lipid-laden macrophages in their lungs, accompanied by signs of lung injury [5]. Lipid-laden macrophages, indicative of pulmonary surfactant damage, were also detected in the BALF of EVALI patients [5, 17, 18]. Vitamin E acetate has also been reported to exert harmful effects on pulmonary surfactant and type II pneumocytes [19]. As a surface-active substance, tocopherol acetate increases surface tension in the pulmonary alveoli, disrupting the dynamics of alveolar compression and expansion during the respiratory cycle. This results in hypoxia and, ultimately, acute respiratory failure [20].

Van Bavel et al. conducted a study to assess the effects of e-cigarette liquids on pulmonary surfactant function using a bovine surfactant model. The study showed that, among e-liquid additives, vitamin E acetate was the strongest disruptor of the lipid bilayer in surfactant, leading to impaired alveolar ventilation [21]. The *in vitro* study exposed human airway progenitor cells to e-cigarette aerosol containing tocopherol acetate. Exposure of *in vitro*–cultured airway mucosa to vitamin E acetate resulted in the formation of lipid droplets on its surface, accompanied by an increase in the number and dilation of goblet cells in response. Although goblet cells synthesize and secrete mucus in response to pollutants entering the respiratory tract, insoluble tocopherol acetate may be difficult to eliminate, leading to its accumulation in the body. The analysed cells exhibited increased synthesis of inflammatory factors, including interleukin-6 (IL-6), chemokine ligand 15 (CCL15), soluble interleukin-6 receptor (IL-6sR), and chemokine ligand 2 (CCL2) [22]. Vitamin E acetate is therefore considered a potentially harmful ingredient in e-cigarette liquids. Further research identifies mechanisms through which it can cause respiratory damage and contribute to EVALI.

Pharmacotherapy

Outpatient treatment is recommended for individuals without comorbidities or respiratory disorders, with oxygen saturation above 95%, access to medical care, and follow-up within 24–48 hours. If the patient's condition worsens, immediate medical attention is required. Hospitalization is recommended for patients with suspected EVALI, particularly those with comorbidities such as chronic obstructive pulmonary disease (COPD) or asthma, which can reduce respiratory reserve and arterial oxygen saturation, increasing the risk of respiratory complications [23].

According to current guidelines, glucocorticoids (GCCs) may be beneficial in treating EVALI. A study conducted among patients in Illinois and Wisconsin reported improved respiratory function in 65% of those receiving GCC therapy. Improvement has also been observed in patients with exogenous lipoid pneumonia (ELP) following steroid therapy, suggesting an inflammatory aetiology of both conditions [24]. It is important to rule out an infectious cause of lung damage, as steroid use in such cases may aggravate the disease [25].

In 2019, the University of Rochester Medical Center (USA), in collaboration with the New York State Department of Health, published a report presenting an algorithm for the rapid identification of patients with suspected EVALI. The algorithm is based on clinical data, including dyspnoea, fatigue, chest pain, tachypnoea, and fever; chest imaging showing bilateral airspace opacification; and a history of e-cigarette or vaping device use within 30 days prior to hospital admission.

According to the report, 12 patients with suspected EVALI were admitted between June 1 and September 15, 2019. Initially, 11 patients received empirical antibiotic therapy for community-acquired pneumonia, with 8 out of 12 patients requiring admission to the intensive care unit for advanced respiratory support. Corticosteroids were given to 67% of patients, with 40 mg of intravenous methylprednisolone given every 6–12 hours and gradually tapered. The total treatment duration was approximately three weeks. However, some patients received prednisone for five days and also experienced symptom resolution, suggesting that therapeutic success may be achieved in less than three weeks [26]. Nonetheless, cessation of e-cigarette use remains the cornerstone of treatment.

Conclusions

E-cigarette sales, and consequently their use, continue to rise each year. Easy availability and prevailing trends have boosted their growing popularity, especially among young people. Curiosity about new flavours appears to be another factor contributing to the growing popularity of e-cigarettes among young people. Despite widely available diagnostic tools, diagnosing EVALI remains a challenge due to its nonspecific symptoms. Medical history, recent use of e-cigarettes in particular, is one of the most important factors in diagnosing EVALI. Although the direct cause of lung damage has not been identified, all patients report using e-cigarettes or vaping products. Vitamin E acetate is considered the primary factor responsible for the development of EVALI, as it decomposes into harmful compounds when heated, causing chemical pneumonia. In addition to symptomatic treatment, systemic corticosteroids are commonly used, with therapeutic efficacy typically assessed after about three weeks.

References

1. Jonas A. Impact of vaping on respiratory health. BMJ, 2022; 378: e065997. doi: 10.1136/bmj-2021-065997
2. Rebuli ME, Rose JJ, Noël A, et al. The e-cigarette or vaping product use-associated lung injury epidemic: pathogenesis, management, and future directions: an official American Thoracic Society Workshop Report. Ann Am Thorac Soc, 2023; 20: 1–17. doi: 10.1513/AnnalsATS.202209-796ST
3. Graczyk M, Pawlak Ł, Lewandowska A. Use of hemp extracts rich in THC and CBD in the chronic pain management. Medycyna Paliatywna/Palliative Medicine. 2024; 16: 15–22. doi: 10.5114/pm.2024.138630
4. Duffy B, Li L, Lu S, et al. Analysis of cannabinoid-containing fluids in illicit vaping cartridges recovered from pulmonary injury patients: identification of vitamin E acetate as a major diluent. Toxics, 2020; 8: 8. doi: 10.3390/toxics8010008
5. Bhat TA, Kalathil SG, Bogner PN, et al. An animal model of inhaled vitamin e acetate and EVALI-like lung injury. N Engl J Med, 2020; 382: 1175–1177. doi: 10.1056/NEJMc2000231
6. Bhave SY, Chadi N. E-cigarettes and vaping: a global risk for adolescents. Indian Pediatr, 2021; 58: 315–319
7. Maessen GC, Wijnhoven AM, Neijzen RL, et al. Nicotine intoxication by e-cigarette liquids: a study of case reports and pathophysiology. Clin Toxicol (Phila), 2020; 58: 1–8. doi: 10.1080/15563650.2019.1636994
8. Winnicka L, Shenoy MA. EVALI and the pulmonary toxicity of electronic cigarettes: a review. J Gen Intern Med, 2020; 35: 2130–2135. doi: 10.1007/s11606-020-05813-29
9. Kligerman S, Raptis C, Larsen B, et al. Radiologic, pathologic, clinical, and physiologic findings of electronic cigarette or vaping product use-associated lung injury (EVALI): evolving knowledge and remaining questions. Radiology, 2020; 294: 491–505. doi: 10.1148/radiol.2020192585
10. Henry TS, Kligerman SJ, Raptis CA, et al. Imaging findings of vaping-associated lung injury. AJR Am J Roentgenol, 2020; 214: 498–505. doi: 10.2214/AJR.19.22251
11. Zeng Y, Zhai XL, Wáng YXJ, et al. Illustration of a number of atypical computed tomography manifestations of active pulmonary tuberculosis. Quant Imaging Med Surg, 2021; 11: 1651–1667. doi: 10.21037/qims-20-1323
12. Blount BC, Karwowski MP, Shields PG, et al.; Lung Injury Response Laboratory Working Group. Vitamin E Acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med, 2020; 382: 697–705. doi: 10.1056/NEJMoa1916433
13. Cuerq C, Bordat C, Halimi C, et al. Comparison of α-tocopherol, α-tocopherol acetate, and α-tocopheryl polyethylene glycol succinate 1000 absorption by caco-2 tc7 intestinal cells. Nutrients, 2020; 13: 129. doi: 10.3390/nu13010129
14. Callahan SJ, Beck E, Warren K, et al. Vitamin E acetate continues to drive cases of EVALI. Chest, 2023; 164: A6375–A6376. doi: 10.1016/j.chest.2023.07.4108
15. Jaegers NR, Hu W, Weber TJ, Hu JZ. Low-temperature (<200°C) degradation of electronic nicotine delivery system liquids generates toxic aldehydes. Sci Rep, 2021; 11: 7800. doi: 10.1038/s41598-021-87044-x
16. Wu D, O'Shea DF. Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. Proc Natl Acad Sci U S A, 2020; 117: 6349–6355. doi: 10.1073/pnas.1920925117
17. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary lipid-laden macrophages and vaping. N Engl J Med, 2019; 381: 1488–1489. doi: 10.1056/NEJMc1912038
18. Christiani DC. Vaping-induced acute lung injury. N Engl J Med, 2020; 382: 960–962. doi: 10.1056/NEJMe1912032
19. Casamento Tumeo C, Schiavino A, Paglietti MG, et al. E-cigarette or Vaping product use Associated Lung Injury (EVALI) in a 15-year-old female patient – case report. Ital J Pediatr, 2022; 48: 119. doi: 10.1186/s13052-022-01314-6
20. Lee H. Vitamin E acetate as linactant in the pathophysiology of EVALI. Med Hypotheses, 2020; 144: 110182. doi: 10.1016/j.mehy.2020.110182
21. Van Bavel N, Lai P, Amrein M, Prenner EJ. Pulmonary surfactant function and molecular architecture is disrupted in the presence of vaping additives. Colloids Surf B Biointerfaces. 2023; 222: 113132. doi: 10.1016/j.colsurfb.2023.113132
22. Manna VJ, Dwyer S, Pizutelli V et al. Utilizing primary human airway mucociliary tissue cultures to model ramifications of chronic e-cigarette usage. Toxicol in Vitro, 2024; 94: 105725. doi: 10.1016/j.tiv.2023.105725
23. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin – Final Report. N Engl J Med, 2020; 382: 903–916. doi: 10.1056/NEJMoa1911614
24. Siegel DA, Jatlaoui TC, Koumans EH, et al. Lung Injury Response Clinical Working Group; Lung Injury Response Epidemiology/Surveillance Group. Update: Interim Guidance for Health Care Providers Evaluating and Caring for Patients with Suspected E-cigarette, or Vaping, Product Use Associated Lung Injury – United States, October 2019. MMWR Morb Mortal Wkly Rep, 2019; 68: 919–927. doi: 10.15585/mmwr.mm6841e3

25. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med, 2019; 200: e45–e67. doi: 10.1164/rccm.201908-1581ST

26. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. Lancet Respir Med, 2019; 7: 1017–1026. doi: 10.1016/S2213-2600(19)30415-1