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Pharmacokinetics of Nicotine Absorption from Vaping Devices

[1]Fahad Saed Alrabie, [2]Ahmed Yahya Alwadani, [3]Amin Mohammed Aljedaani, [2]Ibrahim Mohammed Alharbi, [2]Adel Ali Masoud Alomari, [4]Talal Shuayl Aladhyani, [5]Abeer khalid Alorabi, [6]Areej Omar Basunaid, [7]Ziyad Safar Alotiabi

[1]Pharmacist, Children's Hospital in Taif Health Cluster
[2]Pharmacy technician, Althager Hospital
[3]Pharmacy technician, Iradah and mental health complex - mental services- Jeddah
[4]Pharmacy Technician, Zalm General Hospital
[5]King Abdulaziz specialist hospital, Taif
[6]Pharmacist, King Abdulaziz Medical City- Jeddah
[7]Pharmacist, Althager hospital

Abstract

Electronic nicotine delivery systems (ENDS), also sometimes known as "e-cigarettes," or electronic cigarettes, or e-cigs, are battery-operated electronic gadgets that aerosolize a solution, sometimes known as an e-liquid, that is either nicotine-containing or free from nicotine. It is believed that smokers are more likely to embrace electronic cigarettes as satisfying substitutes for traditional cigarettes if the pharmacokinetic profile is similar to that of cigarettes. The present investigation's objective was to get more information about how experienced users of their own device distribute nicotine from e-cigarettes. This study specifically sought to evaluate the nicotine delivery of various first-generation and advanced e-cigarette devices with that of classic cigarettes. This research also aimed to assess the subjective impact of using various kinds of electronic cigarettes and cigarettes.

Keywords*:* pharmacokinetics, nicotine, vaping, device.

Introduction

Electronic cigarettes, are battery-operated electronic devices that aerosolize a solution, sometimes called an e-liquid, that is either devoid of nicotine or contains nicotine. An electric heating element produces the aerosol when it is manually turned on or when the user blows air through the apparatus. The liquid formulation is vaporized during this procedure, and the vapor subsequently condenses to produce an aerosol. Because e-cigarette users inhale vapourised materials, The activity is frequently called vaping [1].

The majority of e-liquids have different amounts of nicotine in them, according to the particular either a main brand or a subsidiary brand. One important performance metric that has been suggested is the how nicotine is delivered by electronic cigarettes: pharmacokinetics; specifically, the maximum blood concentration (Cmax), the time to reach the highest concentration of blood (Tmax), and the total blood nicotine exposure (measured by the region beneath the time-concentration curve) [2].

It is believed that smokers are more likely to embrace electronic cigarettes as satisfying substitutes for traditional cigarettes if the pharmacokinetic profile is similar to that acquired by smoking cigarettes [3].

Where there are laws governing electronic cigarettes, they frequently have upper limitations on the amount of nicotine allowed in e-liquids. These limits are frequently implemented in an effort to mimic the nicotine delivery seen in tobacco products that burn, as well as in response to worries about the potential toxicity and/or addictiveness of nicotine. For instance, as part of the updated Tobacco Products Directive, the European Union (EU) established particular rules pertaining to electronic cigarettes in 2014 [2].

Unlike the EU, Canada has complied with current chemical regulations and established a 66 mg/mL nicotine limit for e-liquids, based only on the molecule's toxicological characteristics [2].

A growing number of studies evaluating adult consumers' intake of nicotine from electronic cigarettes have been published since these limits on nicotine in e-liquids were implemented [4].

According to the data collected thus far, a number of factors, such as e-liquid nicotine content, device type, and user experience, can affect the uptake of nicotine [5].

As per the Family Smoking Prevention and Tobacco Control Act, the US Food and Drug Administration (FDA) is in charge of tobacco products; but, at the moment, it has no control over the production, promotion, or retailing of e-cigarettes. Despite stating that it will establish authority over e-cigarettes, the FDA has not yet reached a final determination [6].

It is critical to comprehend These gadgets' possible misuse liability while evaluating the damages that e-cigarettes may cause to individuals and the general public, which are major factors taken into account in the FDA's final e-cigarette rule. The anticipated harm to the public from e-cigarettes is determined by their toxicity, frequency of use, and intensity of use, just like other medications and drug delivery systems. The intensity and prevalence of usage are directly impacted by the abuse liability of e-cigarettes, which is primarily influenced by nicotine delivery and pharmacokinetics [6].

Aim of the study

The goal of the current study was to get more information about how experienced users of their own device distribute nicotine from e-cigarettes. This study specifically sought to evaluate the nicotine delivery of various first-generation and advanced e-cigarette devices with that of traditional cigarettes. This research also aimed to assess the subjective impact of using different types of e-cigarette devices and cigarettes.

Literature review

Both current and past smokers use electronic cigarettes, or "e-cigarettes," on a regular basis these days. To determine whether and how these products may affect smoking behavior, it is critical to gain as much insight as possible into the attributes of users and their habits of usage [7].

Figure (1) Diagram showing the exterior features and components of the EVP that was tested [18].

The parts are, from left to right, the mouthpiece, the atomizer, the capsule with the e-liquid inside, and the housing with an LED indicator on the side [18].

Vaping characteristics

E-cigarettes can be divided into three main groups, or generations: first-generation "cig-alike" devices with pre-filled cartridges that are typically thrown away after 200 puffs; second-generation models with refillable tanks; and third-generation "mods," or products that have been altered by the user [8].

Additionally, studies indicate that e-cigarette users with refillable tanks might be happier with their devices than those with pre-filled ones. Furthermore, According to online polls of vapers, those who have never smoked may be more inclined to use refillable "mods" and less likely to use pre-filled "cig-alikes" than those who smoke now. Also, it appears that pre-filled devices are more popular with novice users those who use an e-cigarette for the first time than with seasoned users those who have been vaping for a few weeks or months. Nevertheless, these results were all derived from different user samples rather than representative samples, thus it would be helpful to replicate these findings in further samples [9].

Aside from these results, there aren't many comprehensive analyses comparing users of various e-cigarette models or explanations of the methods and motivations behind user modifications of e-cigarettes and e-liquids. To better inform consumers, producers, physicians, and regulators, a more comprehensive understanding of the traits of vapers and the variations among users of various e-cigarette kinds is necessary. Psychiatric illnesses and substance misuse, in particular, are more common in smokers compared to the whole populace. Since nearly all vapers are current or past smokers, it would be helpful to know if these issues are also common among vapers [8].

Figure (2) E-cigarette generations [19].

E-liquid Composition

Depending on the e-liquid formulation, puffing schedule, and device settings, the complex mixture of gasses and particles that makes up e-cigarette aerosol has a different composition. This study looked at common aerosols produced by a third-generation apparatus in response to puff time [10].

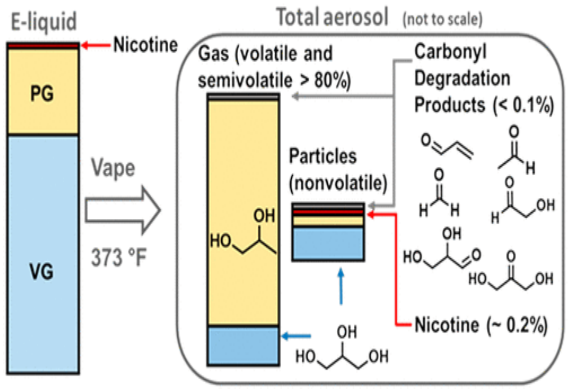

Figure (3) composition of e-liquid [10].

Aerosolized PG, VG, nicotine, optional flavors, free radicals, and a range of carbonyls or hydroxy carbonyls (such as formaldehyde, acetaldehyde, hydroxy acetone, and acrolein) produced by thermal degradation during the e-liquid heating process make up the gas and particle emissions from e-cigarettes [11].

Because heating e-liquid solutions with metal coils causes thermal degradation processes and variations in concentration, coil temperature and e-liquid composition will directly affect the aerosol emissions from e-cigarettes [12].

Another crucial factor that may have an impact on the rates of thermal breakdown in different coil designs is coil surface area. Most research that have been published have linked e-cigarette emissions to the voltage and power of the device, but not directly to the temperature of the vaping coil, which controls the thermal degradation process [13].

Puffing behaviour

Numerous variables, including puff count, puff duration, puff volume, puff velocity, and inter-puff interval, make up vaping topography. Users' grouping or clustering of puffs is a part of their vaping pattern. Previous research has demonstrated that users of e-cigarettes vape seldom, taking most of their puffs in small clusters during ad libitum access. This causes blood nicotine levels to rise gradually rather than quickly. As an alternative, users can take a cluster of puffs, which is a series of close-to-one puffs that give nicotine in a near-bolus dose that causes blood nicotine levels to peak quickly [14].

Different e-liquid flavors have different vaping topographies and usage patterns, which affect how much e-liquid is used and how much nicotine is exposed throughout the body. These variations in vaping behavior between e-liquid flavors are probably caused by mechanisms such as subjective liking, nicotine effects, and e-liquid-related sensory impacts. The greatest indicators of the quantity of e-liquid drank were the number of puffs and the degree of puffing in bigger groups of puffs [15].

Nicotine pharmacology

In both JUUL and regular cigarettes, nicotine, an alkaloid obtained from tobacco plants, is the source of dependency. Rewarding effects on mood, cognition, stress, and anxiety are facilitated by the release of several neurotransmitters by nicotine [16].

When exposed to nicotine, dopamine is released, and over time, the brain's nicotinic cholinergic receptors (nAChRs) are upregulated. Most of the pleasurable effects of nicotine use are attributed to dopamine release, however, it is believed that overexpression of nAChRs contributes to the development of tolerance and physical dependency. [17].

The rate at which nicotine enters the brain affects the potential for abuse of tobacco products. The lungs and arterial circulation are the fastest routes via which nicotine enters the brain. The modern American combustible cigarette is made of tobacco that has been mostly flue-cured rather than air-cured, making it inhalable (pH 5.5–6) and capable of supplying nicotine to the brain in as little as 15–20 seconds. Fast delivery leads to minute-by-minute dose titration, quick reinforcement of behavior, and increased nicotine concentrations reaching the brain [21].

High arterial levels of nicotine produced by rapid delivery also mitigate the effects of tolerance and enable users to continue experiencing the psychological impacts of nicotine throughout the day. Over the course of four to six hours, blood levels of nicotine increase, plateau during the day, and then drop overnight [17].

Despite the fact that nicotine only has a two-hour half-life on average, frequent daily smoking exposes smokers to nicotine all the time. Continuous nicotine exposure increases the likelihood of experiencing withdrawal and tolerance signs of dependence [17].

Nicotine absorption

After starting to smoke, the nicotine from tobacco cigarettes enters the lungs quickly, travels to the brain in a matter of seconds, and manifests as venous Cmax within 5 to 8 minutes. When nicotine is administered by smokers of tobacco cigarettes can titrate nicotine and its related physiological effects while they smoke since the pulmonary route causes blood and brain nicotine levels to rise quickly [6].

Because of this, smoking tobacco cigarettes is the most effective way to get nicotine. All subjects, with one exception, experienced Cmaxes that were in line with previous reports at 2 or 5 minutes after puffing on an e-cigarette. This suggests that nicotine from e-cigarettes is similarly quickly absorbed in the lungs, enabling titration of nicotine through different user behaviors and most likely leading to dependence [6].

Blood transport of nicotine (pharmacokinetics of e-cigarettes)

The capacity of different e-cigarettes to transfer nicotine to users' blood varies significantly, in addition to differences in aerosolization and nicotine content. As might be predicted from the previous discussion of nicotine yield, a number of variables, including as device power, liquid nicotine content and composition, and user puffing behavior, can affect the nicotine delivery of e-cigarettes [19].

As a point of reference for the discussion that follows, the range of the maximal plasma nicotine concentration (Cmax) after one tobacco cigarette is 10 to 30 ng/ml (see the leftmost panel of Figure (4)). Furthermore, the period of maximal concentration (Tmax), which gauges the delivery speed, occurs five to eight minutes following the onset of smoking (venous sample). [19].

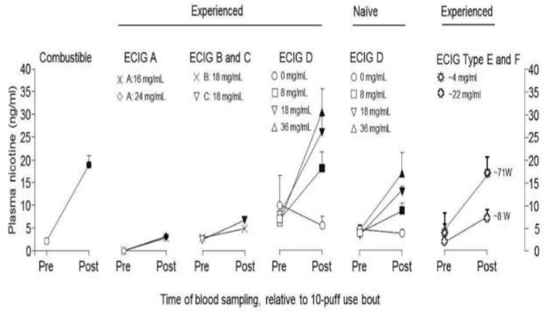

Figure (4) Variability in e-cigarette nicotine delivery [19].

After a controlled puffing session, the pharmacokinetic profile of some e-cigarettes resembles that of tobacco cigarettes (i.e., it exhibits a rapid rise in plasma concentration followed by a steady decrease), much like a bolus dose of nicotine [6].

Nevertheless, studies on the pharmacokinetics of nicotine during ad lib e-cigarette use have revealed a variety of curve shapes, with some users exhibiting intermittent dosing as opposed to bolus dosing (i.e., taking fewer puffs more frequently, which results in a slower increase in plasma nicotine throughout the duration of ad lib use) [6].

This study emphasizes how different users and devices have distinct use patterns, which leads to variable nicotine delivery patterns. Numerous investigations have evaluated the impact of device attributes, such as liquid nicotine concentration and power, users' puffing patterns (referred to as "puff topography"), and their prior device experience on the delivery of nicotine [19].

Device power and nicotine delivery

As with nicotine yield, the power output of the device has a significant role in forecasting nicotine delivery, in addition to nicotine content, form (freebase vs. salt), and puff duration. The power of a device, which depends on coil resistance and battery power, has a significant role in deciding how much nicotine is administered to a user; the variations in nicotine delivery between high power/low nicotine and low power/high nicotine devices serve to emphasize this point [20].

Nicotine delivery based on users' experience

It's important to note that user behavior may be important because some research included people who had little to no experience using e-cigarettes, whereas the study that demonstrated higher nicotine delivery comprised users who had experience. Therefore, a significant element influencing the outcomes of pharmacokinetic investigations appears to be research participants' prior experience with tested e-cigarette devices [19].

Vapers and smokers

There is also some research that compares the levels of nicotine in blood samples from vapers and smokers. In smokers who had never used EC previously, first-generation "cig-a-like" EC delivered nicotine very slowly and in small doses, suggesting buccal absorption as opposed to pulmonary absorption. Because there is evidence that familiarity with EC boosts nicotine consumption, studies where experienced vapers utilize their EC ad-lib are likely to yield more enlightening results [22].

In contrast, a single cigarette's plasma nicotine concentrations typically range from 15 to 20 ng/ml. In one research, one hour of ad-lib vaping produced nicotine concentrations as high as 14 ng/ml, and in another, up to 16 ng/ml. Five minutes after starting a fairly intense puffing regimen prescribed for smokers who had never used EC before, the venous blood nicotine levels attained with 8, 18, and 36 mg of liquid were 9, 13, and 17 ng/ml; in a similar experiment conducted with experienced vapers, the levels were 18, 26, and 36 ng/ml [22].

Aside from the puffing properties and user experience, the kind of EC is probably going to be a big factor. In one study, more sophisticated refillable electronic cigarettes with larger batteries provided nicotine more effectively than a "cig-a-like." Time of maximal nicotine concentration (Tmax) is normally reached by cigarettes in a matter of minutes, whereas early first-generation EC took 20 minutes to reach Tmax [22].

Expert vapers who used their own EC, mostly tank systems, and followed a controlled puffing schedule had a maximum plasma nicotine concentration (Cmax) of just 8 ng/ml on average; nevertheless, the Tmax was 5 minutes. In a recent study, proficient vapers were able to achieve even higher amounts of vapor production utilizing an advanced vaping device with 24 mg/ml e-liquid (44 ng/ml after 1 h) [22].

Nicotine metabolism

Three main metabolic pathways are involved in the metabolism of nicotine in humans: cotinine is produced through further metabolism of the Δ1',5'-iminium ion result of nicotine 5'-oxidation. The most significant nicotine metabolic pathway in terms of quantity is the production of cotinine. Nicotine metabolism is also aided by three secondary pathways: oxidative N-demethylation, 2'-oxidation, and methylation of the pyridine nitrogen to the nicotine isomethoniumion [23].

Similar to nicotine, cotinine is metabolized via three main pathways: Cotinine N-glucuronidation, cotinine N-oxidation, and 3'-oxidation to 3'-hydroxycotinine [23].

Twelve urine nicotine metabolites have been found in addition to cotinine. The fourteenth potential urine metabolite, 5'-hydroxycotinine, is displayed. The estimated percentage of each metabolite in smokers' urine who do not have a P450 2A6 or UGT2B10 deficiency is shown [23].

Health Hazards

There is insufficient data on the effects of ECs on human health because of the wide range of products available and the small number of research that have been done. Numerous symptoms, such as headache, nausea, suffocation, dizziness, altered bronchus gene expression, decreased nitric oxide synthesis in the lungs, and an increased risk of lung cancer, have been linked to enhanced exposure to ECs, according to researchers [24].

The main carcinogens found in EC vapor include formaldehyde, nickel, chromium, nitrosamines specific to tobacco, and acetaldehyde. Furthermore, the main components of the e-liquid in the cartridge, glycerin and propylene glycol, may irritate the respiratory system and eyes. Inhaling these compounds repeatedly or for an extended period of time in an industrial setting may also affect behavior, the central nervous system, and the spleen [24].

The American Chemistry Council has recommended against using these substances to generate fog in theaters due to their potentially dangerous effects and the likelihood of repeated damage to the central nervous system [24].

Additionally, recent research has shown that EC vapor is oxidative and cytotoxic, impairing alveolar macrophage function. In light of this, the researchers have questioned the widely held belief that ECs are safe [24].

Conclusion

When it comes to providing high levels of systemic retention and nicotine levels that are either higher or equivalent to those of tobacco cigarettes, e-cigarettes can be extremely effective nicotine delivery systems. After 15 puffs, the average plasma nicotine Cmax was lower than the data available from smoking a single tobacco cigarette, indicating that not all of the nicotine inhaled and retained is being absorbed through the lungs. Nonetheless, the Cmax of a few of subjects fell within the tobacco cigarette reported range. The usage of e-cigarettes was characterized as pleasurable, raised heart rate, and subjectively decreased cravings to smoke and withdrawal. Pharmacokinetic factors suggest that e-cigarettes have the capacity to cause and maintain nicotine addiction in addition to offering tobacco cigarette consumers a reliable substitute for nicotine.

Because of the potential for explosion, electronic cigarettes pose a hazard to public health comparable to that of traditional cigarettes. There are an increasing number of reports of adverse outcomes occurring from device explosion and burning, as well as complications that arise directly from the compounds contained in the devices. Furthermore, using ECs increases the risk of developing severe lung diseases as reactive pulmonary nodules, respiratory failure, lipoid pneumonia, widespread alveolar hemorrhage, hypersensitivity pneumonitis, organized pneumonia, and bronchiolitis.

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