

Nicotine allergy in correlation with different sources and individual predispositions

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Abstract

Aim: The intensity of allergenic effects after administration of pure nicotine extract from various sources (cigarettes and unprocessed tobacco, tomato, potato, eggplant and bell-pepper) was analyzed in this study.

Methods: Prick and prick-to-prick methods were used to induce dermal allergic reactions and a diameter of the hives was determined. Examinees were divided into two groups: smokers (n=15) and non-smokers (n=15). The study was performed at the Faculty of Science, University of Sarajevo, Bosnia and Herzegovina.

Results: Nicotine from the fruits and tubers did not cause any allergic reaction. Among non-smokers, 20% of respondents had an allergic reaction to nicotine and 7% of smokers were positive to the test. The diameter of the urticaria was the smallest in smokers (3.14 mm), and the highest diameter was detected among non-smokers (4.42 mm). Cigarettes of different manufacturers cause different levels of allergic reactions. A positive correlation was determined between nicotine from cigarettes and untreated tobacco with the size of urticaria.

Conclusion: Nicotine from untreated tobacco caused a stronger allergic reaction compared to nicotine from commercial cigarettes. Nicotine allergy causes a greater diameter of the urticaria in individuals with a previous diagnosis of an allergic reaction to tree and grass pollen.

Keywords: *allergy, Bosnia and Herzegovina, nicotine, prick-test.*

Introduction

From the pharmacological point of view, nicotine is the most powerful tobacco smoke ingredient. Nicotine is a highly toxic alkaloid when it is administered in high concentrations, present in some plants of the Solanaceae family, especially in tobacco (*Nicotiana tabacum L.*). Nicotine is primarily responsible for creating tobacco addiction (1). At low concentrations, it stimulates the central nervous system, leading to adrenaline excretion in the body, while at higher concentrations it becomes a highly toxic compound that has a similar effect as nerve poison and causes general paralysis. The lethal dose for humans is 0.5-1 mg/kg corresponding to the total dose of 30-60 mg for an adult (2). The average cigarette contains about 10 mg of nicotine, of which 1-2 mg is taken by body depending on the type of tobacco, smoke absorption rate, smoke volume, inhalation depth and the size of the rest of the cigarette (1). Nicotine is an oily liquid which, due to auto-oxidation in the air and light, becomes pale-yellow to brown-colored (2,3). By its chemical structure, nicotine is amine formed from pyridine and pyrrolidine ring (3). Nicotine absorption through the biological membrane depends on pH. Nicotine is a weak organic base with pKa 8.0. In its ionized state, it is not absorbed rapidly through bio-membranes (4,5). After absorption, nicotine goes to the bloodstream, where at pH 7.4, 69% of nicotine is ionized. Less than 5% of the total nicotine concentration is bound to blood plasma proteins (4). Based

on autopsies of smokers and nicotine infusions, it has been discovered that the liver, kidneys, spleen, lungs and the brain have the highest affinity for nicotine binding. On the other hand, fatty tissue has the lowest affinity (4,5). It should be noted that nicotine has a high affinity for binding to the nerve tissue and that receptor binding capacity in this tissue is increased in smokers compared to non-smokers (4). This increased binding capacity is the result of a greater number of nicotine cholinergic receptors in the brain tissue of smokers. The nicotine synthesis is done in many plant species, but this process is studied mostly for the genus *Nicotiana* because of the highest accumulation of nicotine in these plants (6). Nicotine is also present in plants which are very present in human diet, primarily tomato, potato, eggplant and paprika. The function of nicotine in these plants is still unknown. However, it is assumed that nicotine in these plants serves as a natural defense against bacteria, fungi, insects and animals (7). The presence of nicotine in fresh food, especially in the family Solanaceae, was first proved in 1986 by Castro and Monji (8). Literature reveals only a few studies on the content of nicotine in food from Solanaceae (Table 1). Also, Malson et al. (2001) have reported that concentration of nicotine in the tobacco of bidi cigarettes (21.2 mg/g) was significantly greater in comparison to nicotine concentrations in commercial filtered (16.3 mg/g) and unfiltered cigarettes (13.5 mg/g) (9).

Table 1. Content of nicotine in food of Solanaceae family

	Castro & Monji, 1986	Sheen, 1988	Davis et al., 1991	Domino et al., 1993	Siegmund et al., 1999
Potato	-	Potato cortex: 1480 µg/kg	Pulp: 15.3±1.7 µg/kg Cortex: 4.8±0.8 µg/kg	7.1±5.9 µg/kg	4.5±2.2 µg/kg
Tomato	6.0±2.4 µg/kg	231 µg/kg	5.1±0.8 µg/kg	4.1±1.8 µg/kg	2.4±1.2 µg/kg
Eggplant	100 µg/kg	265 µg/kg	-	-	1.9±0.7 µg/kg
Green pepper	5.7±0.0 µg/kg	315 µg/kg	-	-	3.7; 5.8; 6.1 µg/kg
Yellow pepper	-	-	-	-	9.0 µg/kg
Red pepper	-	-	-	-	5.9 µg/kg

It has been reported that in some cases nicotine can cause allergic reactions and signs may include: breathing difficulties, swelling of tongue or throat, hives. The aim of the study was to analyze the comparative effect of nicotine originating from different tobacco products (cigarettes from different manufactures and unprocessed tobacco) and various plants (Solanaceae), and to analyses levels of allergic reactions based on the size of urticarias.

Methods

The study included 30 examinees, of which 15 were smokers and 15 non-smokers and it was performed at the Department of Biology, Faculty of Science, University of Sarajevo, Bosnia and Herzegovina. Smokers group included active smokers with more than two and less than 30 years of smoking experience and smoked more than 10 and less than 40 cigarettes per day. In the smokers group, two respondents had allergy to tree and grass pollen, one respondent had seborrheic dermatitis, one mite and house dust allergy. Smoking years were calculated according to the following formula:

$$\text{Pack years} = \frac{\text{Cigarettes per day}}{20} \times \text{smoking experience (years)} \quad (10).$$

The non-smoker group included respondents who never smoked cigarettes or other tobacco products. Two respondents from this group had tobacco allergy, two examinees had asthma, three were allergic to tree and grass pollen, two had a medicinal allergy and one lactose intolerance.

Extraction of pure nicotine

Pure nicotine was extracted from five types of commercially available cigarettes and two types of unprocessed tobacco. Extraction was performed using a method by Pavia et al. (11). The method is based on the usage of 10 g of tobacco which is dissolved in NaOH solution (5%) and filtered by using Buchner funnel. Triple extraction was carried out using the ethoxy-ethane. Drying was done with

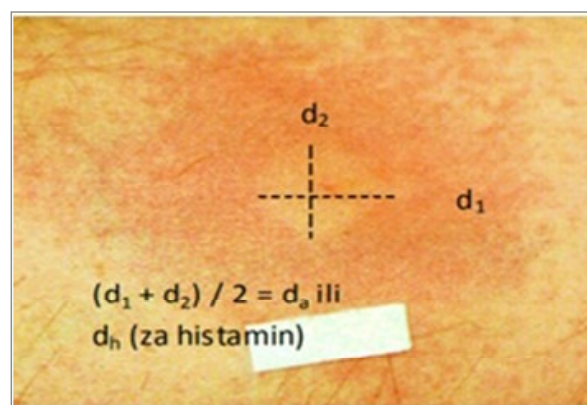
anhydrous potassium carbonate and by evaporating the ethoxy-ethane in a water bath. Picric acid was added and the solution was cooled in an ice bath in order to precipitate nicotine crystals. Crystals were dissolved with distilled water with heating and solution was prepared for further analysis.

Skin prick testing

Analysis was performed by skin prick-test (SPT) (12). Thickness of lancets was 0.9 mm for SPT (Heinz Herenz Medizinbedarf GmbH, REF. 1110106). Prick test was done after the area of the forearm was disinfected with rubbing alcohol (propan-2-ol). A drop of aqueous allergen solution was placed on the forearm and pricked with lancet at an angle of 45° (13). The distance between the allergens was from 1.5 cm (13) up to 2 cm (12). The size of the hive was determined as the average of the longest and the shortest diameter (Figure 1). If dimensions of hive are greater than negative control, then ratio $d_a/d_h > 0$ indicates significant hypersensitivity (12,13).

A prick-to-prick test was used to analyze the allergic reaction to the natural sources of nicotine (food testing). The test involved a direct fruit prick with lancet and its transfer to the skin. Mature and immature tomatoes, potatoes, eggplants and peppers were used for allergy testing.

Figure 1. Calculation of hive's diameter (Radonić, 2011)



Results

Table 2 presents the positive results of prick-tests for smokers and non-smokers, including the mean value \pm STDV of diameter of the urticaria. Results were presented only for examinees with positive prick-test. As a source of nicotine, cigarettes of different brands and unprocessed tobacco were used.

Among smokers (15 examinees), in 27% (4/15) some type of allergic disease has been diagnosed before the prick-test (two had pollen allergy, one seborrheic dermatitis and one had an allergy to mites and house dust). The remaining 11 examinees were healthy. Of all examinees who had some type of allergic disease, only one person with seborrheic dermatitis tested positive to the nicotine prick-test (1/4; 25%). Overall, in the smokers group, 7% (1/15) of examinees tested positive on the nicotine prick-test.

In the non-smokers group (n=15), eight examinees (53%) had some allergic disease before the analysis was performed (two were allergic to tobacco, two had allergic asthma, three had an

allergy to tree and grass pollen and one had drug allergy). Positive prick-test among these eight examinees was detected in one (1/8; 13%), where examinee had the tree and grass pollen allergy. In the group of examinees without diagnosis, positive results to the prick-test were detected in two examinees (2/7; 29%), who suffered from nicotine allergy after the treatment. Overall, in the non-smoker group, 20% (3/15) had reaction after application of the nicotine prick-test.

As it has already been mentioned, 33% of the non-smoking examinees had a positive reaction, while only 7% of the smoking examinees did. The diameter of the urticaria among smokers was the smallest (3.14 mm), although the examinee had a diagnosed skin disease. Non-smokers positive on the nicotine prick-test had a mean diameter of 3.85-4.42 mm. The examinee allergic to tree and grass pollen had the largest urticaria diameter. The severest allergic reaction was detected in persons who were treated with nicotine from unprocessed tobacco (Ia and Ib).

Table 2. Results of prick-test analysis for smokers and non-smokers where nicotine was used as allergen

Source of nicotine	Sample	Non-smokers (20 %) n=15			Smokers (7 %) n=15		
		1. examinee*	2. examinee*	3. examinee [†]	Diameter (mm)	4. examinee [‡]	Diameter (mm)
Cigarettes	I	+	+	+	0.66	+	0.2
	II	+	+	+	0.8	+	0.2
	III	+	+	+	0.73	+	0.2
	IV	+	+	+	0.8	+	0.2
	V	+	+	+	0.73	+	0.2
Unprocessed tobacco	Ia	+	+	+	0.93	+	0.2
	Ib	+	+	+	1.14	+	0.26
Mean \pm stdv		3.85 \pm 0.89	4.00 \pm 0.57	4.42 \pm 0.78	-	3.14 \pm 0.37	-

*Examinees without prior allergic disease, who showed nicotine allergy after prick test;

[†]Examinee with allergy to tree and grass;

[‡]Examinee with seborrheic dermatitis.

Table 3 presents allergic reactions after prick-prick tests. Various types of Solanaceae family were used as the source of allergens.

Table 3. Results of prick-prick tests (natural source of nicotine from the Solanaceae family)

Solanaceae		Tomato	Potato	Eggplant	Pepper
Examinees	Smokers	-	-	-	-
	Non-smokers	-	-	-	-

It was found that none of the four used plants that contain nicotine cause an allergic reaction in both smokers and non-smokers.

Table 4 shows the correlation among all examinees with positive prick-test. Correlation was analyzed in relation to the size of the urticaria.

Table 4. Pearson correlation for the size of the urticaria in examinees with positive prick test

Examinees	Pearson test	Non-smokers			Smokers
		Tobacco allergy (1)	Tobacco allergy (2)	Tree and grass pollen allergy (3)	Seborrheic dermatitis (4)
(1)	R	-	.642	.807*	.560
	Sig	-	.120	.028	.191
(2)	R	.642	-	.734	.764*
	Sig	.120	-	.060	.046
(3)	R	.807*	.734	-	.881 [†]
	Sig	.028	.060	-	.009
(4)	R	.560	.764*	.881 [†]	.560
	Sig	.191	.046	.009	.191

*Correlation is significant at the 0.05 level;

[†]Correlation is significant at the 0.01 level.

Positive correlation in the size of the urticaria was found among all examinees. The size or diameter of the examinees with tobacco allergy (i) positively correlates with the size of the examinee with an allergy to tree and grass pollen, as well as the diameter of the urticaria between the patient with tobacco allergy (ii) and the patients with seborrheic dermatitis ($P < 0.05$). The highest correlation was established for the diameter of the urticaria between examinee with seborrheic dermatitis and examinee with an allergy to tree and grass pollen.

Discussion

Tobacco allergy has been confirmed by a large number of scientific articles. Becker et al. (1976) confirmed the presence of allergen in tobacco

analyzing its effect on rabbits and humans (14). They concluded that 20 cigarettes on average contained between 720 and 1440 μg of nicotine. Lehrer et al. (1986) detected the presence of IgE antibodies from raw tobacco leaves in smokers, non-smokers and former smokers (15). Lee et al. (1998) found that, after administration of nicotine intradermal dose to a nineteen-year-old boy, nicotine could cause urticaria in hypersensitive persons (7). The lack of a large number of scientific papers regarding tobacco and nicotine allergies can be attributed to the weak recognition of this problem by the biomedical community (16).

In our study, pure nicotine was isolated and an allergic reaction was found in several examinees. By analyzing the sought-after response to tobacco allergens using

skin prick tests, it was found that in both groups only four examinees had a positive cutaneous reaction. In this context, it should be emphasized that tobacco, or nicotine as an inhalation allergen, do not belong to the relatively frequent causes of allergies. Hypersensitivity to tobacco, bacteria, fungi and plant fibers was confirmed in less than 10% of the allergic people or less than 5% of the total population tested (17). Bauer and Aleric (2012) analyzed hypersensitivity to conventional inhalation allergens and symptoms in adult patients with clinical allergic rhinitis (17). Out of 456 patients with AR symptoms, 227 had a positive reaction to a skin-prick test (49.7%). Only eight examinees showed hypersensitivity to nicotine. In their study, Belia and Andria (2002) had 49 out of 141 (34.75%) examinees that were positive to one or more allergens. Only two examinees had a positive cutaneous reaction to tobacco (18).

After the testing of urticaria diameter, the highest values were recorded for pure tobacco. Allergic reactions to pure tobacco have already been documented in some earlier researches. Thus, for example, in the research by Ortega et al. (1999), a case of a non-smoker allergic to smoking tobacco and tobacco leaves was noticed (16). Larger diameters of urticarias are likely to be the result of higher nicotine concentrations in this unprocessed tobacco than in factory cigarettes. Due to the lack of scientific papers that would confirm the precise concentration of nicotine in pure tobacco, the attitude of some authors (19) should be mentioned. Every step in the tobacco production that affects the plant metabolism has some effect on the final content of the alkaloids. The highest mean size of urticarias was observed in examinees with allergy to tree and grass pollen (4.42 ± 0.78 mm). Also, allergy cases with a prior diagnosis of allergy to some other allergens are mentioned in literature. The results of the aforementioned research by Ortega et al. (1999) indicate that tobacco can induce IgE mediated responses due to the existence of common antigenic epitopes between tobacco and

amber pulp (16). Authors present a twenty-one-year-old non-smoker with an allergy to tobacco, with previously diagnosed allergic rhinoconjunctivitis and avocado allergy.

Also, positive results of examinees with sebaceous dermatitis are interesting, since they are consistent with the opinion of many authors that smoking can affect different skin diseases. Thus, Bas et al. (2016) wrote in their study that alcohol and tobacco-consuming examinees had a greater predisposition to sebaceous dermatitis (20).

After testing the examinees to natural nicotine sources (mature and unsaturated tomato, eggplant, pepper, potatoes), the cutaneous response of all respondents was negative. It should be said that nicotine is a natural ingredient of some plants that synthesize this alkaloid in endogenous processes (6). The presence of nicotine in fresh food or plants of the Solanaceae family was first discovered by Castro and Monji (8). Nicotine was identified in potato, tomato, eggplant, green, yellow and red peppers by other authors (21-24). Moldoveanu et al. (2016) also had an interesting research which, besides discovering nicotine in the mentioned plant species, also revealed the presence of very small amounts of nicotine in carrots, bananas, pears, apples, blueberries and strawberries (25). It should be noted that some authors attribute the presence of nicotine in the species mentioned in this paper to the environmental pollution with high nicotine content or the nicotine-containing pesticides being used (6).

Species of Solanaceae family contain a low concentration of nicotine and do not cause an allergic reaction. The severity of an allergic reaction correlates with the concentration of nicotine in various tobacco products. The highest concentration of nicotine is present in unprocessed tobacco, which also causes the gravest allergic reaction. Nicotine-induced allergic reaction is more severe in examinees with an allergic reaction to pollen.

Conflicts of interest: None declared.

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