

# THE EFFECT OF THE TYPE OF INHALED ANTI-ASTHMATIC THERAPY ON THE PROPERTIES OF SALIVA IN CHILDREN – A PHANTOM STUDY

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## ABSTRACT

**INTRODUCTION:** Asthma is the most common chronic childhood disease, mainly treated with inhaled steroid anti-inflammatory drugs (ICSs) and inhaled bronchodilators. Unfortunately, current literature emphasizes their negative effect on the condition of soft tissues of the oral cavity and hard dental tissues.

**OBJECTIVES:** The aim of the study was to assess the effect of types of inhaled anti-asthmatic drugs on the properties of saliva in children.

**MATERIAL AND METHODS:** Study group included 114 asthmatics and 94 healthy patients between the age of 3 and 17. Information about the age of onset, severity of asthma, use of anti-asthmatic medications, duration of the therapy, method of drugs' administration, and number of their application were recorded. The severity of asthma was assessed by a pediatrician. Saliva was collected for resting pH, buffering capacity, hydration, saliva quantity, and viscosity measurements using saliva-check buffer kit (GC). Student's *t*-test,  $\chi^2$  test, Mann-Whitney *U* test, and Spearman's correlation coefficient were used, with a significance level of  $p < 0.05$ .

**RESULTS:** Asthmatics appeared to be characterized by significantly lower average values of saliva quantity ( $p = 0.0064$ ), buffering capacity ( $p = 0.0002$ ), and viscosity ( $p = 0.0094$ ) than controls. Spearman's rank correlation revealed a negative correlation between steroid dose, therapy duration, and the use of dry powder inhalers (DPIs) on saliva quantity. Moreover, combination therapy with  $\beta_2$ -agonists and DPIs reduces hydration of lip mucosa. Finally, the use of DPIs increases the viscosity of saliva.

**CONCLUSIONS:** The study shows that inhaled anti-asthmatic medications have a considerable effect on salivary properties.

**KEY WORDS:** children, asthma, anti-asthmatic therapy, saliva properties.

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## INTRODUCTION

Asthma, the most common chronic childhood disease, belongs to the group of allergic diseases. It is estimated that asthma affects around 339 million people worldwide; this number is increasing due to global urba-

nization [1-3]. Asthma is characterized by chronic inflammation of the airways, causing contraction of smooth muscle and increased mucus secretion in the bronchial tree. This results in characteristic symptoms, such as sudden attacks of breathlessness, tightness of the chest, coughing, and wheezing breath. Usually, an asth-

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matic attack is sudden and acute, posing a direct threat to patient's life [4]. The treatment of asthma is based on avoiding allergic factors causing exacerbation of the disease, chronic use of long- and short-acting inhaled bronchodilators ( $\beta_2$ -agonists, LABA/SABA), and inhaled steroid anti-inflammatory drugs (inhaled corticosteroids [ICSs]) [4]. Current studies emphasize the adverse and negative local impact of these medications on the condition of soft tissues of the oral cavity and hard dental tissues [5-9]. The most frequently observed problems in the oral cavity include predispositions to the development of tooth decay and tooth wear, oral candidiasis, and the appearance of mucosal erosions and ulcers. It is also believed that inhaled anti-asthmatic drugs may cause xerostomia. Several authors have observed a negative effect of the therapy on the properties of saliva, such as the buffering capacity, and pH flow rate [10-12]. However, other studies have shown no such correlation, which makes the issue still an arguable topic [13-15].

## OBJECTIVES

The aim of the study was to assess the effect of types of inhaled anti-asthmatic drugs on salivary properties in children between 3 and 17 years old.

## MATERIAL AND METHODS

The study group included patients diagnosed with asthma who had been treated with steroid inhaled therapy (ICSs) or combined therapy with  $\beta_2$ -agonists at the Department of Child Pneumonology and Allergology of Medical University of Warsaw. Patients who qualified for the control group were generally healthy, took no medications, and were regularly treated at the Department of Pediatric Dentistry of Medical University of Warsaw. The inclusion criteria for both groups were as follows: age 3-17 years old, cooperation of the patient (permitting for clinical examination), and written consent of the parent/legal guardian and/or the patient to participate in the study. The consent of the Bioethics Committee (No. KB/6/2017) was obtained. The study was carried out during 2017 and 2018. Information about patients' general health status and medications used were based on analysis of patients' medical history and interviews with parents or legal guardians. Information regarding the age of onset, severity of asthma, use of anti-asthmatic medications, and duration of the therapy, method of drugs' administration, and number of their application were recorded. The severity of asthma was assessed by a pediatrician according to GINA classification [16]. Mild asthma was identified in patients requiring low doses of ICSs or as-needed low doses of ICS-formoterol; moderate asthma in cases with low doses of ICS-LABA; and severe asthma in patients with medium to high doses of ICS-LABA.

Salivary properties were tested in each patient using saliva-check buffer kit (GC). Saliva was collected during morning hours, at least 2 hours after a meal. Patients were requested to refrain from brushing their teeth and using antibacterial mouthwashes prior to the examination. Resting pH value, buffering capacity, and saliva composition were assessed using the saliva-check buffer kit (GC). Hydration (time elapsed following the appearance of saliva droplets on the lower lip mucosa, or 60 seconds) and viscosity (1 – watery, clear saliva; 2 – frothy, bubbly saliva; 3 – sticky, frothy saliva residues) were assessed visually. The patient, while chewing paraffin for five minutes in an upright position, was asked to collect saliva in a calibrated sterile tube. pH values of resting saliva were considered normal within a range of 6.8-7.8, moderately acidic within a range of 6.0-6.6, and acidic within a range of 5.0-5.8. Secretion of stimulated saliva in an amount exceeding 5.0 ml, obtained within 5 minutes, was identified as normal; within a range of 3.5-5.0 ml/5 min as low, and in amounts below 3.5 ml/5 min as very low. The buffering capacity of stimulated saliva was estimated according to a colorimetric test strip after 5 min of reaction time (green – 4 points, green/blue – 3 points, blue – 2 points, blue/red – 1 point, red – 0) as normal (10-12 points), as low (6-9 points), or as very low (0-5 points).

## STATISTICAL ANALYSIS

The results were entered into a database and subjected to statistical analysis using Statistica v.13.3 (Student's *t*-test,  $\chi^2$  test, Mann-Whitney *U* test, Spearman's correlation coefficient). The significance level was set at  $< 0.05$ .

## RESULTS

Of 222 children invited for dental examination, 14 were excluded due to a lack of cooperation (8 children), consumption of sweet snacks or drinks prior to examination (2 children), or a lack of a complete medical history or information in the questionnaire (4 children). Ultimately, 208 children were included in the study: 86 (41.3%) girls and 122 (58.7%) boys. Numbers of children examined in the study and from control group are presented in Table 1.

**TABLE 1.** Numbers and percentages of children included in the examination

Parameter	Study group	Control group	All
Number of patients, <i>n</i> (%)	114 (100)	94 (100)	208 (100)
Gender, <i>n</i> (%)			
Male	71 (62.3)	51 (54.3)	122 (58.7)
Female	43 (37.7)	43 (45.7)	86 (41.3)
Average age $\pm$ SD	8.02 $\pm$ 4.95	8.35 $\pm$ 3.69	8.19 $\pm$ 3.83

**TABLE 2.** Age at diagnosis and type and duration of anti-asthmatic therapy

Parameter	
Onset of asthma (months)	
Interval (M)	0.5-154
Average (M ± SD)	39 ± 26.83
Duration of therapy	
Interval (M)	2-183
Average (M ± SD)	58 ± 42.83
Inhaled corticosteroid drug used (ICS), n (%)	
Fluticasone propionate (FP)	92 (80.7)
Budesonide (BUD)	7 (6.1)
Combined therapy (ICSs + long-acting $\beta_2$ -agonists), n (%)	
15 (13.2)	
Method of administration, n (%)	
Metered dose inhaler (MDI)	65 (5.0)
Dry powder inhaler (DPI)	49 (43.0)
Oral anti-inflammatory drugs, n (%)	
Antileukotriene	15 (13.2)
Antihistamine	63 (55.3)
Intermittent use of short-acting $\beta_2$ -agonists, n (%)	
30 (26.3)	

The study group consisted of patients receiving inhaled anti-asthmatic drugs for an average period of  $58 \pm 42.83$  months. In 102/89.5% patients, a mild type of asthma was diagnosed. Most of the patients (92/80.7%) received ICS flutotide (fluticasone propionate – FP). ICS as a monotherapy was undertaken by 86.8% of patients, and 13.2% received combined therapy with long-acting  $\beta_2$ -agonists. Age at asthma diagnosis and duration and type of anti-asthmatic therapy in the study group are presented in Table 2.

Saliva tests using the GC buffer test showed no statistically significant differences between the groups in terms of parameters of resting saliva pH ( $p = 0.9703$ ), hydration ( $p = 0.4026$ ), or quantity of saliva ( $p = 0.2231$ ) (Table 3). In the study group, sticky saliva ( $p = 0.0040$ ) and very low buffering capacity ( $p = 0.0001$ ) were observed significantly more often than in the control group (Table 3). Statistical analysis of average resting saliva pH, buffering capacities, and saliva quantity showed significant differences between the groups in terms of the two latter parameters ( $p = 0.0002$  and  $p = 0.0064$ , respectively) (Table 4).

Statistical analysis indicated significant differences between combined therapy and independent ICS ther-

**TABLE 3.** Saliva properties assessed with GC buffer test

Parameter/Assessment	Study group		Control group		p-fraction	p-value
	n	%	n	%		
Resting saliva pH						
Acidic	18	15.79	15	15.96		0.9703
Moderately acidic	93	81.58	76	80.85		
Normal	3	2.63	3	3.19		
Average value ± SD	6.19 ± 0.613		6.28 ± 0.65			0.1621
Hydration						
Low	88	77.19	77	81.91		0.4026
Normal/high	26	22.81	17	18.09		
Buffering capacity						
Very low	52	45.61	19	20.21	0.0001*	0.0005*
Low	49	42.98	62	65.96	0.0009*	
Normal	13	11.40	13	13.83	0.6652	
Average value ± SD	5.58 ± 1.89		6.57 ± 1.94			0.0002*
Quantity of saliva						
Very low	34	36.56	19	24.36		0.2231
Low	45	48.39	46	58.97		
Normal	14	15.05	13	16.67		
Average value ± SD	4.10 ± 1.86		4.77 ± 1.70			0.0064*
Viscosity						
Watery, clear saliva	56	49.12	61	64.89	0.0225*	0.0094*
Frothy, bubbly saliva	33	28.95	26	27.66	0.8978	
Sticky, frothy saliva	25	21.93	7	7.45	0.0040*	

\*Statistically significant value ( $p < 0.05$ )

**TABLE 4.** Average values and frequencies of saliva properties in the study group

Parameter	n	Resting saliva pH		Buffering capacity		Quantity of saliva		Low hydration		Sticky saliva	
		Average ± SD	p-value	Average ± SD	p-value	Average ± SD	p-value	n (%)	p-value	n (%)	p-value
ICSs therapy	99	6.19 ± 0.61	0.9632	5.65 ± 1.91	0.5434	4.10 ± 1.96	0.4709	18 (18.2)	0.0025*	18 (18.8)	0.0129*
Combined therapy (ICS + β <sub>2</sub> -agonists)	15	6.16 ± 0.647		5.13 ± 1.73		4.13 ± 1.03		8 (53.3)		7 (46.7)	
Method of administration											
MDI	65	6.26 ± 0.58	0.3362	5.71 ± 2.04	0.6409	4.50 ± 1.91	0.0275*	11 (16.9)	0.0846*	10 (15.4)	0.0518
DPI	49	6.09 ± 0.64		5.41 ± 1.67		3.81 ± 1.77		15 (30.6)		15 (30.6)	

\*Statistically significant value (p < 0.05)

**TABLE 5.** Correlations between anti-asthmatic therapy and salivary properties

Average numbers	ICS therapy	Combined therapy (ICS + long-acting β <sub>2</sub> -agonists)	ICS dose	Number of administrations per day	Using DPIs	Duration of ICS therapy	Duration of combined therapy
Buffer test GC							
Resting saliva pH	0.0788	-0.0052	-0.1673	0.1396	0.1005	-0.0853	-0.12254
Hydration	-0.1271	-0.2832*	-0.0311	-0.0385	0.1615	-0.2818*	-0.2796
Buffering capacity	-0.0357	-0.0589	0.0143	-0.0409	0.0452	-0.0086	0.2199
Quantity of saliva	-0.0186	-0.0689	-0.1981*	-0.1106	-0.2099*	-0.2199*	0.4994
Viscosity	0.0497	-0.1825	0.1125	-0.0331	0.2303*	0.0823	-0.1627

\*Statistically significant value (p < 0.05)

apy regarding hydration of lip mucosa and consistency of saliva. The results show a greater frequency of low hydration and sticky saliva in patients on a combined therapy than in those on ICS monotherapy (p = 0.0025 and p = 0.0129, respectively) (Table 4). Moreover, patients using DPIs were characterized by significantly lesser quantities of saliva than patients using MDIs (p = 0.0275) (Table 4). A similar relationship was found in terms of hydration of lip mucosa and consistency of saliva, with the results being close to statistical significance (Table 4).

Spearman’s correlation rank revealed no significant relationships between ICS therapy and saliva properties. According to statistical analysis, the use of combined therapy significantly reduced hydration of the mucosa. Prolonged ICS therapy had a similar effect on this property. Furthermore, Spearman’s correlation showed a weak but significant negative relationship between the average quantity of saliva and ICS dose, duration of monotherapy, and use of DPIs. Also, the use of DPIs significantly increased saliva viscosity (Table 5).

## DISCUSSION

Even though, the published literature has been indicating oral health problems in asthmatic patients for quite some time, no clear consensus was made among

researchers regarding the influence of type of medication, duration of therapy, or frequency and method of administration. The current study showed that patients with asthma on inhaled therapy demonstrated significantly lower buffering capacity, reduced average quantities, and higher viscosity of saliva compared to healthy patients. A similar observation in terms of buffering capacity was made by Mazzoleni *et al.* [10], who recorded 43% of asthmatic patients with low buffer capacity compared to none from control group; in fact, the majority of healthy patients (60%) exhibited high buffer capacities of saliva (p > 0.05). These observations are comparable with the results of the present study, where nearly 45.6% of asthmatics were characterized by “very low” buffering capacities compared to the control group (20.2%). Also, average buffering capacities were significantly lower in the study group (5.58 ± 1.89) than in controls (6.57 ± 1.94) (p = 0.0002). Bairappan *et al.* [11], in a study on 50 asthmatics and 50 non-asthmatics, found a significant reduction in mean buffering capacities between the two groups (p = 0.019). Contradictory results were obtained by Ersin *et al.* [13], Alaki *et al.* [14], and Al-Dlaigan *et al.* [15], who found no differences in buffering capacities between investigated groups. Moreover, Ersin *et al.* and Alaki *et al.* investigated changes in salivary properties in connection with inhaled therapy in asthmatic patients.

Neither team found any correlation between type and duration of therapy, frequency and method of daily administration, and time of drug inhalation. On the other hand, Bairappan *et al.* [11] observed a moderate negative correlation between buffering capacity and severity of asthma ( $r = -0.84$ ), use of combination therapy ( $r = -0.515$ ), and duration of inhaled therapy ( $r = -0.397$ ). Alteration in salivary flow, consistency, and buffering capacity may be due to the impact of  $\beta_2$ -agonists, which, according to some observers, affect salivary glands, resulting in diminished production of saliva [17]. This assumption can be confirmed by the findings of the present study, in which, a negative correlation was observed ( $r = -0.2832$ ) between the use of  $\beta_2$ -agonists and hydration, demonstrating a negative effect of this type of therapy on the salivary gland of lower lip mucosa. However, the present results indicated no correlation between buffering capacity and inhaled anti-asthmatic treatment.

Another frequently described problem in patients with inhaled therapy is xerostomia and diminished saliva flow. In the present study, we observed a reduction in average quantity of saliva in the investigated group compared to the control group ( $p = 0.0064$ ). This result is consistent with the study by Ersin *et al.* [13]. What is more, reduced saliva flow in the asthmatic group was considered the only significant bivariate variable in the development of caries. However, Alaki *et al.* [14] observed no differences between studied groups in terms of saliva production. They recorded a reduction in saliva flow along with an increased severity of asthma, related to medications used by patient. A similar relationship was observed by Arafa *et al.* [18, 19] in two studies assessing the impact of inhaled therapy on the oral health of asthmatic patients. Moreover, apart from the severity of asthma, Bairappan *et al.* [11] found a significant negative relationship between saliva flow on one hand, and combination therapy ( $r = -0.71$ ) and duration of therapy ( $r = -0.531$ ) on the other. Their results are consistent with observations of the current study, as we found a negative correlation between saliva quantity and ICS dose, duration of ICS therapy, and usage of DPIs. However, neither Santos *et al.* [20] nor Al-Dlaigan *et al.* [15] noted any differences in saliva flow between asthmatics and healthy patients. The latter team explained this result in terms of difficulties in collecting saliva in smaller patients. However, they found that patients on combined therapy were characterized by reduced saliva flow rate compared to patients using antihistamine or ICS therapy only ( $p = 0.04$ ). They explained that patients with more severe types of asthma used ICS therapy combined with  $\beta_2$ -agonists, which affected their stimulation of saliva. Such effect was also observed in a study by Sag *et al.* [12] on 28 patients with diagnosed moderate persistent asthma, to whom, a combination treatment with a long-acting  $\beta_2$ -agonist (50 mg salmeterol and 100 mg FP) was administered. Saliva flow was measured before

and after one month of treatment. The authors observed a statistically significant difference between the two measurements ( $p = 0.0015$ ). However, they assumed that the reduction in saliva production was a result of the disease itself, as the treatment period was quite short for such a drastic effect in patients with moderate asthma. Wogelius *et al.* [21] also found an association of  $\beta_2$ -agonists with oral health, especially development of caries. In the present study, no significant relationship was observed between saliva flow and the use of  $\beta_2$ -agonists. These differences in outcomes could be due to the small group of patients on combined therapy in the present study, which involved mostly patients with mild asthma compared to only some with moderate type of asthma. Therefore, lower dosage of inhaled medications may not influence oral health as strongly as initially presumed.

The final examined property of saliva was its resting pH. The results of the current study showed no differences between the group of asthmatics and healthy patients. Nor did the authors observe any correlations between pH value and inhaled therapy. Similar results were obtained by Santos *et al.* [20] and Al-Dlaigan *et al.* [15] studies, where no significant differences were found between two investigated groups. However, Khalifa *et al.* [22] observed a significant reduction in pH value in asthmatic patients compared to control group. This result is consistent with those of Ersin *et al.* [13] and Konde *et al.* [23], who not only found a significant decrease in salivary pH in asthmatics, but also observed a significant effect of inhaled therapy on this value. Ersin *et al.* found a negative correlation between a duration of medication and pH value ( $p = 0.017$ ,  $r = -0.28$ ), whereas Konde *et al.* observed a significant relationship between combination therapy and reduced pH compared to values of patients using salbutamol or ICS independently. Additionally, Arafa *et al.* [18,19] presented a relationship between severity of asthma and pH value of resting saliva, which might also be related to the different types of medications used. Similarly, Bairappan *et al.* [11] showed a negative correlation between salivary pH and severity of asthma, duration of inhaled therapy, and usage of combined therapy. Kargul *et al.* [17] presented the effect of  $\beta_2$ -agonists on the flow and composition of saliva, observing that pH value decreased significantly 30 minutes after drug application. On the other hand, Tootla *et al.* [24] observed no decrease in pH below a critical value of 5.5, which leads to demineralization. However, they learned that DPIs based on lactose as a flavor enhancer caused significantly lower pH values, which may be an important factor leading to the development of cariogenic bacteria and enamel demineralization. This observation is consistent with the result of the current study, as the authors observed a negative correlation between the use of DPIs and quantity of saliva ( $r = -0.209891$ ). Another finding was a positive relationship between DPIs treatment and saliva viscosity, as confirmed by Shashikiran *et al.* [25].

## CONCLUSIONS

The present study shows that inhaled anti-asthmatic medications provide a considerable effect on salivary properties, especially buffering capacity, quantity, and viscosity. Many factors may affect saliva: not only the type of medication, but also its dosage, duration of the therapy, number of applications, and method of administration. As a result, asthmatics are considered to be at high-risk of developing caries, periodontitis, and sudden changes in their bacterial and fungal oral environments. Therefore, it is important to educate patients, parents, and medical specialists regarding the importance of dental care and prophylaxis, in order to improve the quality of life of these patients.

## CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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