

Effect of Cholinergic Receptor Antagonists on the Potentiation of the Effect of Adenosine Receptor Blockers in People with Bronchial Asthma

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The interaction between adenosine receptor blockers and anticholinergic substances in the treatment of bronchial asthma is an area of interest. The efficacy of such combinations in managing bronchial asthma and bronchial hypersensitivity needs to be explored further. Understanding lung function parameters such as airway resistance and intrathoracic gas volume is crucial for evaluating the effects of these medications. Objective: This study aimed to investigate the effect of combining the adenosine receptor blocker, bamifylline, with the anticholinergic substance, ipratropium bromide spray, in patients with bronchial asthma. Specifically, the study sought to assess changes in lung function parameters, including airway resistance and intrathoracic gas volume, after administering ipratropium bromide alone and in combination with bamifylline. Methods: Sixteen patients with bronchial asthma were enrolled in the study. Lung function was evaluated using body plethysmography, with measurements of airway resistance (Raw), intrathoracic gas volume (ITGV), airway specific resistance (SRaw), and airway specific conductance (SGaw). Patients initially received ipratropium bromide inhalation (2 inhalations x 20µg), followed by Raw and ITGV measurements at intervals (5, 30, 60, and 120 minutes). Subsequently, patients received bamifylline (2 x 600 mg) daily for seven days at home. On the eighth day, they were administered ipratropium bromide spray (2 inhalations x 20µg), and lung function parameters were assessed similarly. Results: Administration of ipratropium bromide alone led to a significant reduction in airway resistance ($p < 0.05$). However, the combination of ipratropium bromide with bamifylline did not significantly enhance the effects of adenosine receptor blockade ($p < 0.05$). Specifically, there were no significant changes in Raw, ITGV, SRaw, or SGaw after combining ipratropium bromide with bamifylline. Conclusion: The study findings suggest that the addition of anticholinergic substances did not potentiate the action of adenosine receptor blockers in patients with bronchial asthma. Therefore, the anti-inflammatory effects of xanthines, such as bamifylline, were not augmented by anticholinergic substances in this study. These results highlight the need for further research to explore alternative therapeutic approaches in the management of bronchial asthma.

Keywords: Atrovent (ipratropium bromide); Bronchial asthma; Bamifix (bamifylline).

Asthma, including COPD (chronic obstructive pulmonary disease) as inflammatory airway chronic disorders,

which attack millions of people and result in a significant economic burden on the health care system. Although these disorders have unique

and distinctive features, they manifest continuous inflammation of the airways and remodeling of the wall of the airways that can lead to progressive loss of lung function.¹

Asthma is characterized by progressive and irreversible obstruction of the airways, mucus hypersecretion, and infiltration of neutrophils and macrophages in the lung². The reaction that regulated the type of these chronic illness are unspecified. Adenosine as signaling nucleoside is produced in hypoxic condition in lungs which are inflamed, suggesting that they may play a regulatory role in chronic lung illness³. Adenosine is a purine nucleoside base, commonly known as molecule of adenosine triphosphate, or ATP. The use of adenosine as a pharmacological medicine function through receptors called adenosine purinergic receptors.⁴ Adenosine receptors have four subtypes: A₁AR, A₂AAR, A₂BAR, and A₃AR. These subtypes are targets for the creation of novel asthma medications.⁵

There is a range of documentation to maintain the idea that adenosine has effect in asthma. Adenosine when it is inhaled produce bronchoconstriction in patients with asthma; however not in non-asthmatics⁶. This reaction emerges to be mediated by activation of mast cell, as it can have obstructed by antihistamines and mast cell activation suppressors. Aspirated adenosine causes discharge in bronchoalveolar liquid of mast cell mediators, along with histamine, tryptase and prostaglandin D₂⁷. Adenosine aspirated and adenosine 5-monophosphate and triphosphate are noted to produce bronchospasm in patients with asthma, very likely through the release of mast cell mediators and because the effect has not been determined with adenosine administered intravenously, this indicate that bronchospastic impact is related with the way of the administration. Bronchospasm, which take place with adenosine monophosphate and triphosphate (inhaled) is also related with dyspnea progress⁸.

The muscarinic receptor M₃, the subclass of the cholinergic receptor is accountable for contracting bronchial smooth muscle. Despite the fact ipratropium and other similar substances stops all 5 subtypes of muscarinic receptors with same affinity, antagonism of the M₃ receptor alone may

have dilated effects. Bronchodilatation caused by ipratropium develops gradually and is normally slighter intense than that caused by adrenergic agonists. Asthmatic patients in some causes may exhibit beneficial response that may take up to six hours⁹. An acceptable response to ipratropium can be noticed in the patient with asthma who experience deterioration of psychogenic nature¹⁰.

This study aims to analyse the impact of cholinergic receptor antagonists (ipratropium bromide) in potentiating the effect of adenosine receptor blockers Bamifix (bamifylline) in patients diagnosed with bronchial asthma and COPD.

MATERIAL AND METHODS

Study design

The experimental procedures in this study received approval from the Clinical Ethics Committee of the University Clinical Center of Prishtina, with Protocol Number 502, dated March 22, 2019. The purpose of the examination was explained beforehand to each patient. Retrospective study, performed in 16 patients with bronchial asthma moderate. Average of disease duration was 10 ± 6 years (from 4-20 years). Average of their age was 40 ± 7 years (from 29 – 45 years), whilst average weight was $74 \pm 7\%$ (from 64 – 72%). The patients involved in the study were not admitted to hospitals; however, the tests were conducted in medical settings such as University Clinical Center. The anamnestic data and lung clinical and functional research were used to choose the individuals. There have been examinations, as shown in tables 1, 2, and diagram 1.

Study procedures

Using a minimum of 48 hours of prior research of bronchial reaction, patients have not received bronchodilator substance. The examinees were familiar with the way of functional analysis of the lungs. Patients have suffered from asthma with or without concomitant bronchitis. Each patient has previously been explained the purpose of the examination. Defined was lung activity at rest, which is composed of measurement of the airway resistance (Raw) and the volume of intrathoracic gas (ITGV). From obtained data, was calculated specific resistance and specific airway conductance:

$$SRaw = Raw \times ITGV$$

$$SGaw = 1/SRaw$$

The bronchial response research in various substances was conducted by measuring Raw, and ITGV and SGaw and SRaw are calculated and more of very sensitive indicators of the airways; Medical Research Council¹¹.

On the first day is applied Atrovent- ipratropium bromide (2 inh. 20/μg) and measurements made (Raw, ITGV) after 5, 30, 60, 120 min. Afterwards, administered is Bamifix (2 times 600 mg) for 7 days at home. On the 8th day, the Raw and ITGV measurements were done again, and Atrovent (2 inh. 20/μg) was applied and again After 5, 30, 60, and 120 minutes, measurements were made using ITGV and Raw, and the airways' Specific Resistance (SRaw) and Specific Conductance (SGaw) were computed.

According to certain theories, alterations in the respiratory system are not important, have nothing to do with the onset of bronchial asthma or other obstructive illnesses, and have nothing to do with the symptoms of allergies.

Statistical Analysis

The obtained data are grouped and examined. Utilizing statistical methods of the data involve the measurement of mean values (X), standard deviation (SD), standard error mean (SEM), as well as analyzing the significance of differences between groups of individuals

receiving adenosine receptor blocker treatment and antagonist's cholinergic receptors. The obtained results were analyzed utilizing a test (t-test). The statistical test ANOVA was applied to compare the groups.

RESULTS AND DISCUSSION

Antagonists of cholinergic receptors (ipratropium bromide (2inh. x 20/ig), are applied on the 1stday and are examined changes in the respiratory system with body plethysmography. Registered was the important decrease of the airway's resistance (p<0.05) and to the same patient then applied blockers of adenosine receptors (bamifylline 2 x 600 mg per os) at home for seven days in a row. On day 8, thepatient submitted for the examination of the respiratory system and again administered 1 tablet of bamifylline, and after 60 min measurements performed and again is applied ipratropium bromide 2 inh. x 20/ig, and once again are made the measurements of the respiratory system (Raw, ITGV). Based on the results obtained, there is no further decrease of the specific airway resistance (SRaw) (p<0.05) as shown in figure 1 and 2.

All constitutional data of patients are given in tables 1 and 2 and diagram 1.

Even though the majority of patients can effectively manage their asthma with the present

Table 1. Overall characteristics of the studied patients

n	Age	Height (cm) (years)	Weight (kg)	VC (L) Vital capacity expressed in liters	FEV ₁ (L) Enhanced expiratory volume in the first second, expressed in liters.
16	40 ± 7	170 ± 5.5	74 ± 7%	3.75 ± 0.11	3.66 ± 0.23

Experimental group n = 16; X ± SEM.

Table 2. Characteristics of the participants' body plethysmography in this investigation.

Group	n	Raw (kPa × s/L)	ITGV (L) Volume of in thoracic gas	SRaw (kPa × s) Specific airway resistance	SGaw (kPa × s) Specific airway conductance
Experimental	16	1.13 ± 0.7	3.11 ± 0.5	3.5 ± 0.9	0.28 ± 0.11

Raw (kPa × s/l); Airway resistance (kilo Pascal/sec/liter)

treatments, many asthmatics continue to search for more potent treatments. Comprehending the variability of asthma also implies the necessity of creating novel treatments for specific forms of asthma.

This paper summarizes the current methods of treatment of asthma considering current knowledge of the pharmacology and signaling of adenosine receptor blockers in the treatment of asthma. It also addresses the debate around their use and new avenues for the development of asthma treatments. With this advancement, new treatment modalities can be employed to lessen the global rise in morbidity and death linked to chronic obstructive pulmonary disease and asthma.

The study included 16 patients with bronchial asthma. With the exam of the variables of the respiratory system of all patients, we found increased initial ventilator values such as the specific resistance (S_{Raw}) of the control group treated with anticholinergic substances- ipratropium bromide and the experimental group treated with adenosine receptor blocker administered 7 days at home. On day 8 is assessed the permeability of the airways and again is administered 1 tablet bamifylline; after 60 min performed the Raw and ITGV measurements and is continued by the applying antagonist of cholinergic receptors- ipratropium bromide, and performed the Raw and ITGV measurements after 5, 30, 60, 120 min. There was a significant reduction in the airways' specific S_{Raw} resistance in both groups—the experimental group and the control group, respectively (p<0.05). Airway resistance did not change (p<0.05) even

after 7 days of administration (2x600 mg) of adenosine receptor blockers and stimulation of adenosine receptors with anticholinergic substances. This confirms the fact that blockage of adenosine receptors has no synergist action with the anticholinergic substances and as such are ineffective if administered in combination¹¹⁻¹⁴.

By preventing muscarinic acetylcholine receptors from functioning, acetylcholine is blocked by both short- and long-acting antagonists, which reduce bronchoconstriction¹⁵.

Recently, tiotropium, a structural analogue of ipratropium, is authorized for the management of COPD and emphysema. Tiotropium has a high affinity for all muscarinic receptor subtypes, just like ipratropium, however it releases from these receptors considerably more slowly¹⁶. Tiotropium specifically detaches from muscarinic M₃ receptors considerably more slowly than it does from muscarinic M₂ receptors, according to linkage and function tests. Tiotropium's strong muscarinic receptor affinity and its ability to detach very slowly from them allows the administration of only one dose per day. The ability to slowly detach from the receptor offers a potential benefit by restricting the capacity of elevated levels of endogenous acetylcholine agonists to overcome receptor blockage.

Theophylline belongs to the group of methylxanthines, which causes the decrease of the release of signals that promote inflammation, such as leukotriene and TNF-alpha, and also effectively decreases the inflammation by acting as a direct antagonist of the adenosine

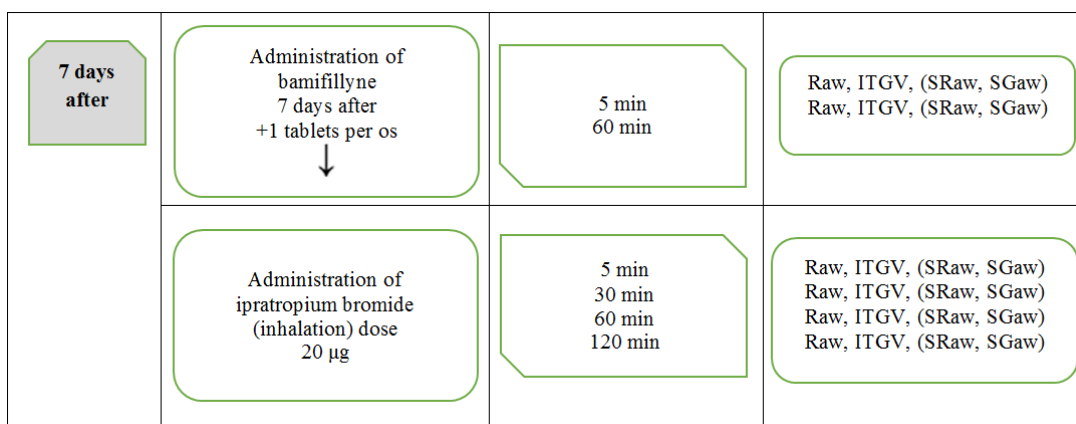


Diagram 1. Study flow chart

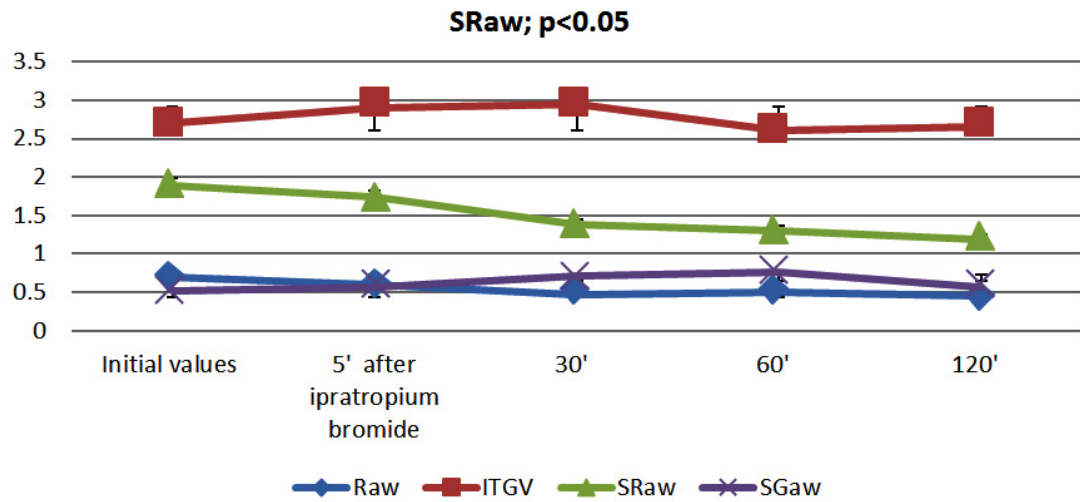


Fig. 1. Effect of anticholinergic substances-ipratropium bromide (2inh x 20µg), in Raw, ITGV, SRaw and SGaw; (n = 8; X ± SEM);

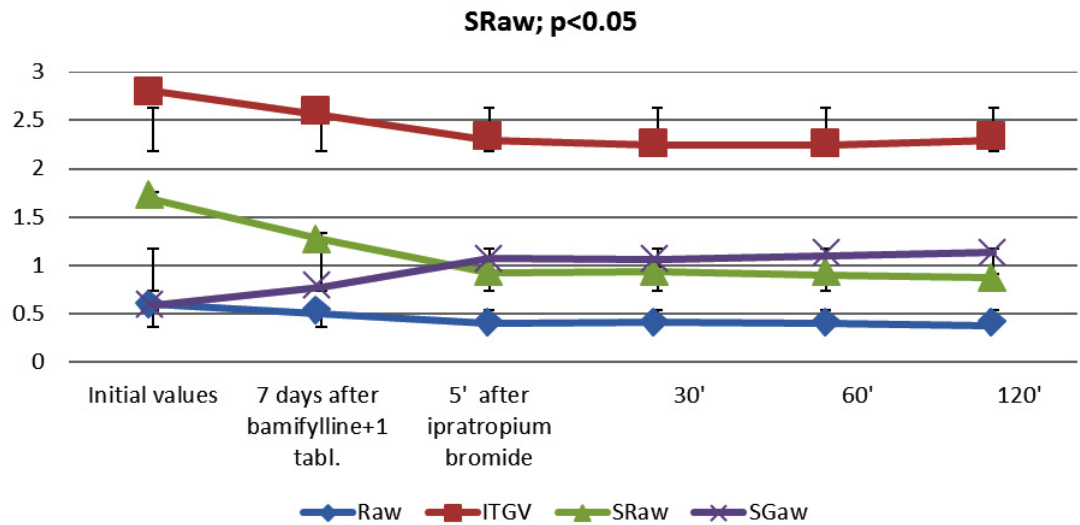


Fig. 2. Effect of anticholinergic substances-ipratropium bromide (2inh x 20µg), in Raw, ITGV, SRaw and SGaw; seven days later administering bamifylline (2 x 600 mg); (n = 8; X ± SEM)

receptors specifically causing smooth muscle relaxation and bronchiole enlargement by reducing airway respiratory obstruction¹⁷, whereas anti-inflammatory medicines (glucocorticoids) reduce activation and infiltration of lymphocytes, eosinophils, and mast cells in bronchialmucosa¹⁶. Each of these medicines has a unique mechanism of action¹⁸

Adenosine, a purine nucleoside base also recognized as adenosine triphosphate (ATP),

functions pharmacologically through adenosine purinergic receptors, including four subtypes: A₁AR, A₂AAR, A₂BAR, and A₃AR, which are targeted for the development of new asthma medications.

These receptors belong to the family of G protein-linked receptors and are expressed in a variety of cells including most immune cells, further implying adenosine’s function in regulating immune cell activity¹⁹.

The biological response to adenosine is mediated by four receptors bound to a G protein. Adenosine A₁ and A₃ receptors attach to Gi/0, while adenosine A_{2A} and A_{2B} receptors attach to Gs, resulting in the activation of phospholipase C, through Gq/11. Furthermore, adenosine A₁, A₃, and A_{2B} receptors can activate both K1 and Ca12 channels, whereas cAMP-independent intracellular pathways are also described [20].

The activity of receptors of adenosine A₁ increases in the smooth muscles and epithelium of asthmatics' airways. In the tissues of the human respiratory tract and HBSMC, activation of receptors A₁ AR causes effects such as hyperreactivity of the respiratory tract. Activation of A₁ AR leads to increased expression of the mucus hypersecretory MUC2 gene in human airway epithelial cells. Moreover, pro-inflammatory effects are produced when A₁ AR is activated in a variety of human cells²¹⁻²⁵.

Furthermore, evidence from research and clinical settings indicates that adenosine A₁ AR receptors are a key target in asthma. In Europe, bamifylline, an A₁ AR antagonist, is authorized for the management of asthma. Theophylline inhibits human phosphodiesterase enzymes at a therapeutic plasma level that is less than what would cause adenosine AR receptor antagonism, which is why it has anti-asthmatic benefits in humans²⁶. Substantial experimental data suggest that adenosine acts as an anti-inflammatory agent, to understand the manner of activation of the various ways of adenosine receptors in specific situations of the disease, will help with the administration of agonists and specific receptor antagonists in the treatment of various inflammatory disorders.

Because A_{2A} receptor activation results in anti-inflammatory actions that open the door to asthma treatment, these receptors are particularly interesting. There have been several reports of adenosine A_{2A} AR receptors' anti-inflammatory properties²⁷. Furthermore, human monocytes secrete the pro-inflammatory cytokine interleukin IL12 and block the degranulation of mast cells caused by Fc[R1 when A_{2A} receptors are activated. Additionally, T cell effects, neutrophil adherence to endothelium, and neutrophil activation and degranulation are all suppressed by activation of the receptor A_{2A}²⁸.

Recently, regadenoson has been

demonstrated to be safe for administration among patients with COPD and asthma. Another substance, apadenoson, is still in the stage of research for asthma and COPD²⁹.

Activation of A_{2B} AR may cause broncho-relaxing and anti-inflammatory effects, because of a rise in cyclic AMP levels inside cells. Increases in cyclic intracellular AMP are well recognized to reduce inflammation, relax bronchial smooth muscle and bronchodilation, and stop endothelial cell alterations that would otherwise enhance endothelial permeability. Now it is reported that the use of antagonists A_{2B} AR can increase the permeability of the endothelium³⁰.

Strong antagonists of the adenosine A₃ receptor have been created to treat inflammatory illnesses including asthma. Activation of A₃ receptors is done by inducing phospholipase C and inhibiting adenylate cyclase. In addition to inducing inflammation, A₃ agonists also stimulate phospholipase D and release histamine and other inflammatory mediators from mast cells. These factors have led to the recommendation that adenosine A₃ receptor antagonists be administered clinically to treat inflammatory illnesses like asthma.³¹

The potential function of stimulation of adenosine A₃ receptors in the pathophysiology of asthma leads toward the development of a selective antagonist of the adenosine receptors A₃ SSR161421. SSR161421 is a nanomolar adenosine A₃ antagonist receptor. SSR161421 has recently been shown to have significant *in vivo* pharmacological activity against specific and allergic patterns of adenosine A₃ ligand in rodents and pigs³²

Acknowledging the part played by adenosine receptors in the development of chronic inflammatory illnesses of the respiratory system raises the possibility of inhibiting these receptors, which can be a useful therapeutic strategy for COPD and bronchial asthma. Today made intensive researches on adenosine receptors concerning the therapy of asthma and (COPD), and identified are a variety of inflammatory cell types, such as neutrophils, macrophages, lymphocytes, and eosinophils, which are crucial to the treatment of bronchial asthma¹⁹.

The study's limitations encompass aspects such as a small sample size, potential biases

in participant selection, specific demographic characteristics of the study population, variability in individual responses to medications, the duration of follow-up, and the breadth of outcomes evaluated.

CONCLUSION

According to the obtained results, the following can be concluded:

Blockers of adenosine receptors - bamifylline given on a daily basis at the dosage of 2 x 600 mg tablets, oral route, results in a notable reduction in the specific airway resistance (SRaw), ($p < 0.05$).

Anticholinergic substance Atrovent (ipratropium bromide - 2 inh x 20 ig) as a result of the effect, not emphasized the effect of bamifillyne by not causing a further decrease of the specific airway resistance (SRaw), ($p < 0.05$).

This implies that the function of anti-inflammatory of the adenosine receptor blockers has not changed the response after administration of anticholinergic substances, reduction of transcription of pro-inflammatory genes caused with the xanthine substance, after application of the anticholinergic substance has not caused a further decrease of specific resistance (SRaw) of the airways.

AUTHOR CONTRIBUTIONS

“Conceptualization, L.M., H.I. and F.A.; methodology, L.M.; software, M.H.; validation, L.M., H.I. and F.A.; formal analysis, L.M., A.D. and D.B.; investigation, L.M., H.I., F.A. and D.B.; resources, A.D.; data curation, L.M. and A.D.; writing—original draft preparation, L.M., H.I. and D.B.; writing—review and editing, L.M., H.I., A.D. and D.B.; visualization, F.A. and F.A.; supervision, L.M.; project administration, L.M. and P.I.; funding acquisition, L.M.. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Data Availability Statement

No new data were created for this review.

Ethics of Human and Animal Experimentation

All experimental procedures of this study were approved by the Clinical ethics committee of University Clinical of Prishtina. Protocol no. 502. Date 22.03.2019

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