Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2020 Jul 15; 8(B):597-601.
https://doi.org/10.3889/oamjms.2020.3894
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Pulmonology*

Effect of Glucocorticoids Following Application of Adenosine Receptor Blockers in Patients with Chronic Obstructive Bronchitis and Bronchial Asthma

Driton Shabani[1], Lirim Mustafa[2], Pellumb Islami[3], Ali Iljazi[4], Arta Dauti[5], Hilmi Islami[6]*

[1]Department of Pharmacy, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosovo; [2]Institution KFLM, Agim Ramadani, Prishtina, Kosovo; [3]Department of Clinical Toxicology, Hospital of Mitrovica, Kosovo; [4]Kosovo Occupational Health Institute, Clinical Centre N.N., Gjakovo, Kosovo; [5]QKUK – Clinical Centre, Prishtina, Kosovo; [6]Department of Pharmacology, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosovo

Edited by: Ksenija Bogoeva-Kostovska
Citation: Shabani D, Mustafa L, Islami P, Iljazi A, Dauti A, Islami H. Effect of Glucocorticoids Following Application of Adenosine Receptor Blockers in Patients with Chronic Obstructive Bronchitis and Bronchial Asthma. Open Access Maced J Med Sci. 2020 Jul 15; 8(B):597-601. https://doi.org/10.3889/oamjms.2020.3894
Keywords: Bronchial asthma; Chronic obstructive pulmonary disease; Budesonide; Fluticasone; Doxofylline
***Correspondence:** Hilmi Islami, Department of Pharmacology, Faculty of Medicine, University of Prishtina, Clinical Centre, Prishtina, Kosovo, E-mail: islamihilmi@hotmail.com
Received: 17-Oct-2019
Revised: 09-Apr-2020
Accepted: 13-Apr-2020

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests

Abstract

AIM: The effects of the glucocorticoids (GR) fluticasone and budesonide and a blocker of the adenosine receptor in the treatment of patients with chronic obstructive pulmonary disease (COPD) and bronchial asthma were studied in this work.

METHODS: The parameters of lung function were determined with body plethysmography. Airway resistance (Raw) was registered and measured and the intrathoracic gas volume and specific resistance (SRaw) of the airways were also calculated.

RESULTS: The results of this study of patients with COPD and bronchial asthma used doxofylline as a blocker of the adenosine receptor. Doxofylline was given orally on 7 consecutive days at home with a dose of 2 × 400 mg orally. Raw and IGTV were then measured, and SRaw was calculated. The results indicated a significant decrease in the airway specific resistance ($p < 0.05$). On the 8th day, the same patients were given two inhalations with spray fluticasone and budesonide (budesonide, 2 inh × 2 mg; Pulmicort 2 inh × 125 mcg). After the inhalations were given, Raw and IGTV were measured after 5, 15, 30, 60, and 120 min, SRaw was then calculated.

CONCLUSION: After the preliminary application of doxofylline, the GRs fluticasone and budesonide have a significant effect ($p < 0.01$) on the decrease of the airway SRaw. This effect suggests that the blocking effect of the adenosine receptor ($p < 0.05$) emphasizes the bronchodilation effect of GRs ($p < 0.01$).

Introduction

According to recent medical literature, significant importance is attributed to caffeine, namely, its capability to block adenosine receptors. Adenosine receptors act through G-protein, and thus intensively studied the possibility of new syntheses and their introductions to therapies with specific blockers, which are more effective to such receptors. Adenosine causes the contraction of the airway's smooth muscles and increases the release of histamine by mastocytes [1].

It is well known that adenosine plays an important role in control of the central nervous system as well as the cardiovascular, pulmonary, and endocrine systems. Adenosine receptors are divided into four subtypes: A_1, A_2, A_3, and A_4. Receptor A_1 is present in all the smooth muscles of the vascular system [2] mediates the inhibition of creation of adenylate cyclase and is responsible for bronchoconstriction. Adenosine receptor A_1 also promotes sleep by inhibiting the cholinergic neuron of the basal part of the frontal brain region [3], whereas receptor A_2 mediates the stimulation of adenylate cyclase and is therefore responsible for bronchodilation [4].

Xanthine derivatives, such as caffeine and theophylline, act as non-selective antagonists to the lung, heart, and brain receptors A_1 and A_2. As such, these derivatives shave an adverse effect on adenosine, causing stimulation, or acceleration of the heart rate [5]. These compounds act as inhibitors of phosphodiesterase (PDE) due to additional anti-inflammatory effects. These effects are useful for the treatment of bronchial asthma but are less appropriate for research purposes [6].

The presence of adenosine receptor A_{2A} in some tissues, such as immune cells, the endothelium and the smooth muscles of blood vessels, has been reported in the literature. Furthermore, iRNK for receptor A_{2A}, to a large extent, is present in the spleen, eye, skeletal muscles, lung, heart, and uterus [7], [8], whereas the physiological role of the adenosine receptor A_{2B} is found in astrocytes, fibroblasts, and blood vessels as well as in the gastrointestinal tract [9], [10].

Adenosine receptor A_3 is recognized in terms of its specific distribution and expression in different types. For example, adenosine receptor A_3 is widely found in sheep and humans but is less present in mice. The pharmacological profile of adenosine receptor A_3 in humans is like that of sheep [11], [12]. In humans, the expression of adenosine receptor A_3 is very high in the lungs and liver, and lowest in the aorta and brain [13]. In the central nervous system, adenosine receptor A_3 has been studied in neurons and glial cells [14].

In comparison to other adenosine receptors, the least is known about receptor A_3.

Adenosine receptor third subclass A_3 is found in the heart and lungs of sheep, and interaction with these receptors leads to the inhibition of adenylate cyclize [15], [16], [17].

The aim of this paper is to study the effect of glucocorticoids (GR) (fluticasone and budesonide) after the preliminary application of blockers of adenosine receptor (doxofylline, 400 mg tablet) in the treatment of patients with bronchial asthma and chronic obstructive pulmonary disease (COPD).

Materials and Methods

Fourteen patients with bronchial asthma and increased bronchial reactivity were examined for this study. For at least 48 h before the study of bronchial reactivity response began, the patients were not given any bronchodilation substances. The participants were informed regarding the method of the functional pulmonary tests. Patients in this study had been diagnosed with asthma, with or without associated COPD. The aim of the examination was explained to each patient in advance. Pulmonary function, composed of measurement of vital capacity, forced expiratory volume in the first s, resistance in the airways (Raw), and intrathoracic gas volume (ITGV) were defined at rest.

The overall quantity of ITGV was measured with the plethysmography method, including non-ventilated closed gas. If the residual functional capacity is taken from ITGV by plethysmography, information regarding the quantity of closed gas due to a severe obstruction, cystic lungs, or pneumothorax will be gained. In healthy subjects with normal pulmonary function, the volume of the intrathoracic gas is equal to the residual functional capacity. From the beta and alpha angles, assisted by tables, values of the airway resistance and volume of the intrathoracic gas were calculated. From gained values, specific resistance was calculated:

$$SRaw = Raw \times ITGV$$

Raw and ITGV were taken for analysis and used to calculate the specific resistance (SRaw). Research on the bronchial response to different substances was performed with the measurements of Raw, ITGV, and SRaw as very sensitive indicators of lung function. The basic and pulmonary function features of the research are provided in Table 1.

Doxofylline, as a blocker of the adenosine receptor, was administered for 7 consecutive days (2 × 400 mg orally). On the 8th day, Raw, ITGV, and SRaw were calculated. Furthermore, on the 8th day, two inhalations of spray fluticasone or budesonide were applied to the same patients (budesonide, 2 inh. × 2 mg; Pulmicort, 2 × 125 mcg inh). Raw and IGTV were measured after 5, 15, 30, 60, and 120 min; SRaw was then calculated.

Our hypothesis was that changes in the respiratory system are not important, not related to the development of bronchial asthma or other obstructive diseases, and not related to allergic manifestation.

The results were pooled and analyzed. Statistical data processing included determination of average values (X), standard deviation, standard mistake (SEM), and testing of the importance of changes in the group of patients treated with adenosine receptor blockers. The results were tested with a t-test. To compare groups, the statistical test ANOVA was used. Potential mistakes with the t-test were avoided with the use of ANOVA.

Results

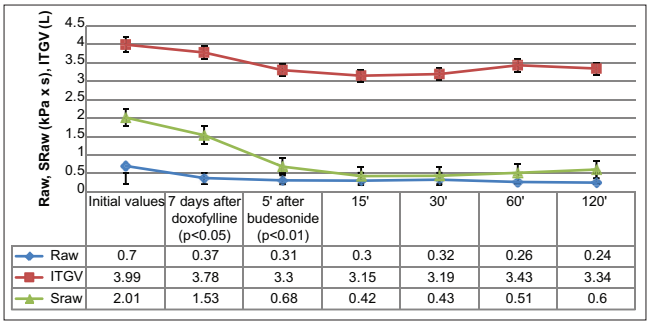
The results of this research in patients with COPD and bronchial asthma indicate that doxofylline, a blocker of adenosine receptors, caused a significant decrease in the airway specific resistance when applied on 7 consecutive days at home with a dose of 2 × 400 mg orally caused a significant decrease in the airway specific resistance ($p < 0.05$) (Figures 1 and 2).

On the 8th day, the same patients were given two inhalations with spray fluticasone and budesonide (Pulmicort, 2 × 125 mcg inh; budesonide, 2 inh × 2 mg). Raw and ITGV were then measured after 5, 15, 30, 60, and 120 min; next, SRaw was calculated. After the preliminary application of doxofylline, the GRs

Table 1: Basic airway characteristics

n	Age (years)	Height (cm)	Weight (kg)	VC (L)	FEV, (L)	Raw (kPa L/s)	ITGV (L)	SRaw (kPa L/s)
14	54 ± 1.75	177.1 ± 1.4	75.21 ± 0.7	3.2 ± 2.5	2.85 ± 2.8	0.7 ± 0.3	3.99 ± 1.95	2.79 ± 1.05

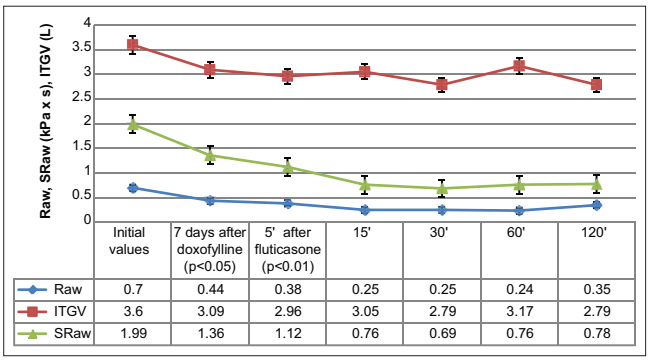
Generalized mean values for: VC (L) and FEV1 (L) are also given. VC: Vital capacity expressed in liters, FEV1 – Enhanced expiratory volume in the first second, expressed in liters. Raw (kPa × S/L); ITGV (L); SRaw = Raw × ITGV; SGaw = 1/SRaw. Raw – Airway resistance expressed in kilo pascal/second/liter, ITGV – Volume of intrathoracic gas expressed in liters, SRaw: Specific airway resistance which is the relationship between resistance and the volume of intrathoracic gas. ITGV: Intrathoracic gas volume.



	Initial values	7 days after doxofylline (p<0.05)	5' after budesonide (p<0.01)	15'	30'	60'	120'
Raw	0.7	0.37	0.31	0.3	0.32	0.26	0.24
ITGV	3.99	3.78	3.3	3.15	3.19	3.43	3.34
Sraw	2.01	1.53	0.68	0.42	0.43	0.51	0.6

Figure 1: Effects of doxofylline and glucocorticoids: Budesonide (2 inh × 25 mg) in raw, intrathoracic gas volume, and specific resistance; 7 days after administration of doxofylline (2 × 400 mg); (n = 7; X ± SEM)

fluticasone and budesonide showed a significant effect ($p < 0.01$) on the decrease of airway SRaw. Following the administration of the respective substances, there were no changes in the heart rate ($p > 0.1$), (Figure 3).

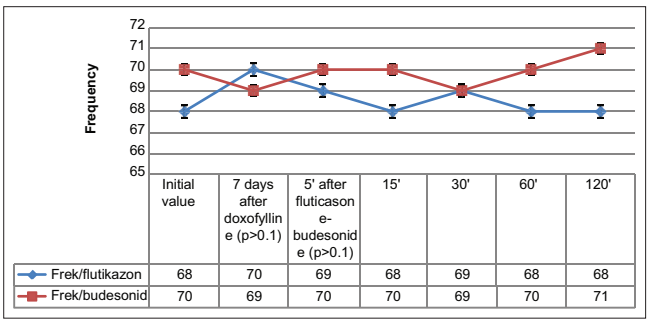


	Initial values	7 days after doxofylline (p<0.05)	5' after fluticasone (p<0.01)	15'	30'	60'	120'
Raw	0.7	0.44	0.38	0.25	0.25	0.24	0.35
ITGV	3.6	3.09	2.96	3.05	2.79	3.17	2.79
SRaw	1.99	1.36	1.12	0.76	0.69	0.76	0.78

Figure 2: Effects of doxofylline and glucocorticoids: Fluticasone (2 inh × 125 mcg) in Raw, intrathoracic gas volume, and specific resistance; 7 days after administration of doxofylline (2 × 400 mg); (n = 7; X ± SEM)

Discussion

Methylxanthines are efficient in asthma treatment, but the mechanism of action is not yet clear. Doxofylline is a partially competitive antagonist to adenosine receptors. Adenosine may act as an autacoid and transmitter of many biologic effects. Observations that are of importance to asthma are those where adenosine can cause bronchoconstriction in



	Initial value	7 days after doxofylline (p>0.1)	5' after fluticasone-budesonide (p>0.1)	15'	30'	60'	120'
Frek/flutikazon	68	70	69	68	69	68	68
Frek/budesonid	70	69	70	70	69	70	71

Figure 3: Effects of doxofylline and glucocorticoids (fluticasone and budesonide) on heart rate; (n = 14; X ± SEM)

asthmatics and emphasize release of immunologically triggered mediators from human mast cells. Therefore, blockage of the adenosine effect should be considered when efforts are made to explain the effect of theophylline [2].

Doxofylline relaxes the smooth muscles of the airways effectively, and this bronchodilation may contribute to its acute therapeutic efficiency in asthma [18].

The antagonisms of both the adenosine receptor and the inhibition of PDE can play a role in its bronchodilation effect. Adenosine does not contract the smooth muscle of human bronchi directly, but after being inhaled it acts as a powerful bronchoconstrictor to asthmatics. Thus, inhibition of the adenosine function can contribute to triggered bronchodilation due to theophylline in some of the asthmatics. The activation of subtype A_{2B} of the adenosine receptor causes some pro-inflammatory effects, and both theophylline and enprofylline are powerful competitive antagonists of the A_{2B} adenosine receptor [12].

Our previous results indicate that because of blockage of the adenosine receptor (doxofylline), bronchomotor tonus was reduced significantly ($p < 0.05$) [19]. Blockers of the adenosine receptor at applied doses of 400 mg did not cause significant change in heart rate and decrease of the systolic and diastolic blood pressure ($p > 0.1$) [20].

The anti-inflammatory effect of doxofylline may also appear as a consequence of its capability to activate deacetylases in the core. Theoretically, deacetylation of histones can reduce the transcription of some pro-inflammatory genes and potentiate the effect of corticosteroids. Research on the development of pharmaceutical preparations is geared toward finding safe corticosteroids, i.e., corticosteroids, which after oral administration has less bioequivalence, less absorbed by lungs, and reduced intensity of in activation in systemic circulation [21]. All inhaled corticosteroids currently in use are absorbed by the lungs and penetrate the systemic circulation, while high doses can also cause systemic reactions [22], [23], [24].

Short-term research has shown a significant slower development in child growth during their 1st year of life [25]. Unfinished studies conducted in children aged 4–8 years after the completion of a medium dosage of inhaled corticosteroids significantly slowed the development of female children [26], [27].

Corticosteroids achieve their effect by regulating the transcription of some genes. Their anti-inflammatory effect is achieved by acting on the repressive transcription factors, called transpression, while their side effects (endocrine and metabolic) are caused by other mechanisms of transactivation [28], [29]. The effect of corticosteroids (i.e., dissociated corticosteroids) has led to research on the separation of the anti-inflammatory mechanism from the mechanism responsible for side effects.

Recent research has shown that the synthesis of such dissociated corticosteroids has the best safety profile possible. For example, the RU486 antagonist has greater transpression capability from transactivation, as do some standard steroids (fluticasone propionate and budesonide) [30]. Other steroids, such as RU24858 and RU40066, also have this capability. At *in vivo* conditions, such corticosteroids have a strong transpression effect but only a small transactivation effect [31], which indicates the possibility of synthesizing high-profile oral steroids for the treatment of inflammatory diseases. Mice research models show that the anti-inflammatory effect of GR substance A is a transcription factor for corticosteroids. Substance A, as a dissociated corticosteroid (does not act in the transactivation), does not induce Mitogen-activated protein kinases phosphatase 1, unlike dexamethasone. This substance activates the GR receptors by causing only the function transrepression that inhibits the lymphocyte Th2 inflammation, thus suppressing the STAT6 translocation induced by interleukin-4 cytokines [32], [33]. Other molecules with steroid dissociation properties, such as ZK245186 and BOL-303242-X, are in the research phase [34]. In the current study, therapy with inhaled GRs for patients who still had asthma symptoms was administered, and agonists of β_2-adrenergic receptors may be added to the steroid regimen for long duration with good results. Once frequently used, today methylxanthines are administered less frequently due to the modest effects and narrow therapeutic window. Selective inhibitors of PDE4, which may have the same efficiency but with fewer side effects, are being assessed in clinical trials. Other new agents aim to affect specific mechanisms, which are important in the commencement and progression of asthma. These mechanisms include blockers of the adenosine receptor and the leukotriene receptor, and therapy with anti-IgE, and omalizumab.

Conclusion

Based on our research results, we can conclude as follows:

- Doxofylline: Blockers of adenosine receptors were applied orally for 7 consecutive days at a dose of 2 × 400 mg, caused a significant decrease in the SRaw of airways ($p < 0.05$)
- GRs: After preliminary application of doxophylline, budesonide and fluticasone have a significant effect ($p < 0.01$) on the decrease of the airways' SRaw.

This finding suggests that the blocking effect of adenosine receptors emphasizes the bronchodilator effect of GRs. Thus, finding confirms the idea that the activation of deacetylation of histones in the cell core (effect of xanthine substances) can decrease the transcription of some pro-inflammatory genes and potentiate the effect of corticosteroids.

References

1. Fredholm BB, Persson CG. Xanthine derivaties as adenosine receptor antagonists. Eur J Pharmacol. 1982;87(4):673-6. https://doi.org/10.1016/0014-2999(82)90359-4
   PMid:6288418
2. Tawfik HE, Schnermann J, Oldenburg PJ, Mustafa SJ. Role of A_1 adenosine receptors in regulation of vascular tone. Am J Physiol Heart Circ Physiol. 2005;288(3):H1411-6. https://doi.org/10.1152/ajpheart.00684.2004
   PMid:15539423
3. Elmenhorst D, Meyer PT, Winz OH, Matusch A, Ermert J, Coenen HH, *et al*. Sleep deprivation increases A_1 adenosine receptor binding in the human brain: A positron emission tomography study. J Neurosci. 2007;27(9):2410-5. https://doi.org/10.1523/jneurosci.5066-06.2007
   PMid:17329439
4. Baraldi PG, Tabrizi MA, Gessi S, Borea PA. Adenosine receptor antagonists: Translating medicinal chemistry and pharmacology into clinical utility. Chem Rev. 2008;108(1):238-63. https://doi.org/10.1021/cr0682195
   PMid:18181659
5. Osadchii OE. Myocardial phosphodiesterases and regulation of cardiac contractility in health and cardiac disease. Cardiovasc Drugs Ther. 2007;21(3):171-94. https://doi.org/10.1007/s10557-007-6014-6
   PMid:17373584
6. Ito K, Lim S, Caramori G, Cosio B, Chung KF, Adcock IM, *et al*. A molecular mechanism of action of theophylline: Induction of histone deacetylase activity to devrease inflammatory gene expression. Proc Natl Acad Sci USA. 2002;99:8921-6. https://doi.org/10.1073/pnas.132556899
   PMid:12070353
7. Dixon AK, Gubitz AK, Sirinathsinghji DJ, Richardson PJ, Freeman TC. Tissue distribution of adenosine receptor mRNAs in the rat. Br J Pharmacol. 1996;118(6):1461-8. https://doi.org/10.1111/j.1476-5381.1996.tb15561.x
   PMid:8832073
8. Peterfreund RA, MacCollin M, Gusella J, Fink JS. Characterization and expression of the human A2A adenosine receptor gene. J Neurochem. 1996;66(1):362-8. https://doi.org/10.1046/j.1471-4159.1996.66010362.x
   PMid:8522976
9. Feoktistov I, Murray JJ, Biaggioni I. Positive modulation of intracellular Ca^{2+} levels by adenosine A2b receptors, prostacyclin, and prostaglandin E1 via a cholera toxin-sensitive mechanism in human erythroleukemia cells. Mol Pharmacol. 1994;45(6):1160-7.
   PMid:8022409
10. Corset V, Nguyen-Ba-Charvet KT, Forcet C, Moyse E, Chédotal A, Mehlen P. Netrin-1-mediated axon outgrowth and cAMP production requires interaction with adenosine A2B receptor. Nature. 2000;407(6805):747-50. https://doi.org/10.1038/35037600
    PMid:11048721
11. Linden J, Taylor HE, Robeva AS, Tucker AL, Stehle JH, Rivkees SA, *et al*. Molecular cloning and functional expression of a sheep A3 adenosine receptor with widespread tissue

distribution. Mol Pharmacol. 1993;44(3):524-32.
PMid:8396714

12. Salvatore CA, Jacobson MA, Taylor HE, Linden J, Johnson RG. Molecular cloning and characterization of the human A3 adenosine receptor. Proc Natl Acad Sci U SA. 1993;90(21):10365-9. https://doi.org/10.1073/pnas.90.21.10365
PMid:8234299
13. Jacobson KA. Adenosine A3 receptors: Novel ligands and paradoxical effects. Trends Pharmacol Sci. 1998;19(5):184-91. https://doi.org/10.1016/s0165-6147(98)01203-6
PMid:9652191
14. Fredholm BB, Irenius E, Kull B, Schulte G. Comparison of the potency of adenosine as an agonist at human adenosine receptors expressed in Chinese hamster ovary cells. Biochem Pharmacol. 2001;61(4):443-8. https://doi.org/10.1016/s0006-2952(00)00570-0
PMid:11226378
15. Dunwiddie TV, Diao L, Kim HO, Jiang JL, Jacobson KA. Activation of hippocampal adenosine A3 receptors produces a desensitization of A1 receptor-mediated responses in rat hippocampus. J Neurosci. 1997;17(2):607-14. https://doi.org/10.1523/jneurosci.17-02-00607.1997
PMid:8987783
16. Von Lubitz DK. Adenosine and cerebral ischemia: Therapeutic future or death of a brave concept? Eur J Pharmacol. 1999;365(1):9-25. https://doi.org/10.1016/s0014-2999(98)00788-2
PMid:9988118
17. Chen GJ, Harvey BK, Shen H, Chou J, Victor A, Wang Y. Activation of adenosine A3 receptors reduces ischemic brain injury in rodents. J Neurosci Res. 2006;84(8):1848-55. https://doi.org/10.1002/jnr.21071
PMid:17016854
18. Scott JP, Peters-Golden M. Antileukotriene agents for the treatment of lung disease. Am J Respir Crit Care Med. 2013;5:538-44.
PMid:23822826
19. Morina N, Haliti A, Iljazi A, Islami D, Bexheti S, Bozalija A, *et al*. Comparison of effect of leukotriene biosynthesis blockers and inhibitors of phosphodiesterase enzyme in patients with bronchial hyperreactivity. Maced J Med Sci. 2018;6(5):777-81. https://doi.org/10.3889/oamjms.2018.187
PMid:29875845
20. Hyseini K, Iljazi A, Morina N, Iljazi F, Islami H. Comparison of methylxanthines (doxofylline and diprophylline) effect in patients with bronchial hyperreactivity and bronchial asthma. Res J Pharm Biol Chem Sci. 2017;8(5):500-9. https://doi.org/10.5455/aim.2016.24.16-19
21. Lajqi N, Ilazi A, Kastrati B, Islami H. Comparison of glucocorticoid (budesonide) and antileukotriene (montelukast) effect in patients with bronchial asthma determined with body plethysmography. Acta Inform Med. 2015;23(6):347-51. https://doi.org/10.5455/aim.2015.23.347-351
PMid:26862243
22. Barnes PJ. Inhaled corticosteroids. Pharmaceuticals. 2010;3(3):514-40.
PMid:27713266
23. Barnes PJ. Corticosteroid therapy for asthma. Pulmo RJ. 2012;21:53-9.
24. Anthracopoulos MB, Priftis KN, Russell G. Safety of inhaled corticosteroids. Why the variation in systemic adverse effects? Curr Pediatr Rev. 2008;4:198-215. https://doi.org/10.2174/157339608785856018
25. Adams N, Lasserson TJ, Cates CJ, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Cochrane Database Syst Rev. 2007;4:CD002310. https://doi.org/10.1002/14651858.cd002310.pub4
PMid:17943772
26. Guilbert TW, Mauger DT, Allen DB. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. J Allergy Clin Immunol. 2011;128(5):956-63.e1-7.
PMid:21820163
27. Wolthers OD, Walters EG. Short-term lower leg growth in 5-to 11-year-old asthmatic children using beclomethasone dipropionate inhalers with chlorofluorocarbon or hydrofluoroalkane propellants: A 9-week, open-label, randomized, crossover, noninferiority study. Clin Ther. 2011;33(8):1069-76. https://doi.org/10.1016/j.clinthera.2011.06.015
PMid:21784529
28. Adcock IM, Barnes PJ. Ligand-induced diff erentiation of glucocorticoid receptor (GR) transrepression and transactivation. Biochem Soc Trans. 1996;24(2):267S. https://doi.org/10.1042/bst024267s
PMid:8736925
29. Vayssiere BM, Dupont S, Choquart A. Synthetic glucocorticoids that dissociate transactivation and AP-1 transrepression exhibit antiinflammatory activity *in vivo*. Mol Endocrinol. 1997;11(9):1245-55. https://doi.org/10.1210/me.11.9.1245
PMid:9259316
30. Barnes PJ, Karin M. Nuclear factor-kappaB: A pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. 1997;336:1066-71. https://doi.org/10.1056/nejm199704103361506
PMid:9091804
31. Reber LL, Daubeuf F, Plantinga M. A dissociated glucocorticoid receptor modulator reduces airway hyperresponsiveness and inflammation in a mouse model of asthma. J Immunol. 2012;188(7):3478-87. https://doi.org/10.4049/jimmunol.1004227
PMid:22393156
32. Liberman AC, Antunica-Noguerol M, Ferraz-de-Paula V. Compound dissociated glucocorticoid receptor modulator, inhibits T-bet (Th1) and induces GATA-3 (Th2) activity in immune cells. PLOS One 2012;7(4):35155. https://doi.org/10.1371/annotation/12a8fc89-5f47-4bad-8863-863d99a0e52d
PMid:22496903
33. Schäcke H, Zollner TM, Döcke WD. Characterization of ZK 245186, a novel, selective glucocorticoid receptor agonist for the topical treatment of infl amatory skin diseases. Br J Pharmacol. 2009;158:1088-103. https://doi.org/10.1111/j.1476-5381.2009.00238.x
PMid:19422381
34. Zhang J, Cavet M, Meid KR. BOL-303242-X, a novel selective glucocorticoid receptor agonist, with full anti-inflammatory properties in human ocular cells. Mol Vis. 2009;15:2606-16.
PMid:20011631