Comparison of Glucocorticoid (Budesonide) and Antileukotriene (Montelukast) Effect in Patients with Bronchial Asthma Determined with Body Plethysmography

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ABSTRACT
Objective: Effect of glucocorticoids—budesonide and antileukotriene—montelukast in patients with bronchial asthma and bronchial increased reactivity was studied in this work. Methods: Parameters of the lung function are determined with Body plethysmography. Raw and ITGV were registered and specific resistance (SRaw) was also calculated. Results: Results of this research, in patients with bronchial asthma, indicate that glucocorticoids—budesonide (Pulmicort; 2 x 2 mg inh) has significant action (p<0.01) on reduction of the specific resistance (SRaw) of airways, applied to the same patients 3 days after administration of montelukast, at home (2 x 10 mg). Three days after administration of the montelukast, antileukotriene medicine, at home, on the fourth day same patients administered a capsule of montelukast, 10 mg dose per os, and significantly (p<0.05) reduced the increased bronchomotor tonus; and the effect of the control with salbutamol (beta2-adrenergic agonist) is effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), (p<0.01). Conclusion: This suggests that the bronchodilator effect of glucocorticoids is more powerful than of the leukotriene, because glucocorticoids terminate the early stage of chemical mediator release (prostaglandins PgD2, SRS, and leukotriene LTC4, LTD4, LTE4 and Cytokinins also etc.) as powerful bronchoconstriction substances, whilst antileukotriene substances does not have this feature.
Key words: Respiratory system, budesonide, montelukast.

1. INTRODUCTION
Bronchial asthma is an obstructive disease of the airways caused by the smooth bronchial muscles contraction, obstruction of which has diffuse nature and improves spontaneously or after the medical treatment. In the core of this process lies the fact of mastocytes degranulation and release of active substances (such Histamine, LTD-4, LTC-4, SRS etc.) in the bronchial micro environment under the effect of antigen.

First of all, during the development of allergic asthma comes to the activation of the immune response, which includes T helper (Th) cells of the type 2. Sensibility commences when genetically predisposed people are exposed to allergens such: pollen or protein of the house dust, including contribution of the environment, such atmospheric pollution. These allergens come in the contact with dendritic cells and Th helper lymphocytes, which further causes development of lymphocyte Th2 forms that:

Create and release the cytokinins, and induces B cells/plasma cells to start generate IgE.

Creation of cytokinins such e.g. Interleukin–5 (IL–5), which starts differentiation and activation of eosinophils,

Creation of other cytokinins (e.g. IL–4 and IL–13), which induce the expression of IgE receptors, mainly in mastocytes, but also in eosinophils; IL–4 also induces the expression of receptors in the endothelium where specifically binds eosinophils.

System is activated in this way, and another repeated exposure to respective allergens would cause attack of the bronchial asthma.

In the early stage of allergic asthma (namely initial response to the provocation with allergen) appears vehemently and most often provokes the spasm of the smooth musculature of the bronchial tree. Allergens react with IgE an-
tibodies fixed to the mastocytes, which cause release of many
spasmoden substances from cells such: histamine, cys-
lein-leukotrienes (LTC-4 and LTD-4) and prostaglandins D-2
(PgD-2) (1,2).

From other mediator released are also IL-4, IL-5, IL-13,
inflammatory macrophage protein – 1 alpha and necrotizing
alpha tumor factor (TNF-alpha).

Obviously, asthma caused from the physical load causes the
manifestation of the above described phenomenon.

Second, later stage or postponed response begins after a pe-
riod of the exposure to certain inducers, thus, it can mani-
fest also by the night. Essentially, this stage is a progressive
inflammatory reaction, which starts in the first period of the
attack, since Th2 lymphocytes are of critical importance.
Manifested inflammatory reaction is different from the re-
action that appears for example in the bronchitis. Specifics
of this reaction is manifestation of ordinary infiltrates of
the inflammatory process supplemented with the activation
of the infiltrate of Th2 lymphocytes released by cytokinins,
and with the activation of the eosinophils. Th2 lymphocytes
and eosinophils have the protection role against any microor-
ganism. In asthma, these cells activated inadequately, where
released are cysteinyl-leukotriene, cytokinins IL-3 and IL-5,
chemokines IL–8 and toxic protein, cationic eosinophil pro-
tein, major basic protein and eosinophil neurotoxin. All of
these substances play an important role in the later stage
of asthma in development of toxic protein, which damage and
destroy the epithelium (3).

Asthma is related with the inflammation and hyperactivity
in airways and acute bronchoconstriction. Glucocorticoids
do not relax directly smooth muscles of the airways, thus,
have little effect on the acute bronchoconstriction. On the
other side, these agents, even alone, are efficient in the inhi-
bition of the airways inflammation. Only a small number of
inflammation mechanism avoided inhibitory effect of these
medicines (4). Anti-inflammatory effects of glucocorticoids
in asthma include modulating of the cytokines and chemok-
ines; inhibition of synthesis of eicosanoids; inhibition of the
basophils, eosinophils and other leukocytes accumulation in
the lung tissues and decrease of the vascular penetration (4).

Asthmatic patients treated with inhaled glucocorticoids
show improvement of symptoms and decrease of the needs
for use of β2 agonists (3).

Antileukotrienes (antagonists of leukotriene receptor) are
newest form of anti-inflammatory medicine. Contact an-
tigen-antibody results in degranulation of mastocytes and
release of mediator substances; LTC-4, LTD-4 and LTE-4,
which cause appearance of the bronchoconstriction in asthma.
From the power of their effect, major and clinical manifesta-
tion of asthma depends. There are two types of leukotriene:
antagonists of the receptor and inhibitors of the synthesis.
Some of antileukotriene called also modifiers of leukotriene.
Antileukotriene blocks the effect of the component, which
manifest contraction of smooth muscles, and block the accu-
mulation of the inflammatory cells, edema, and mucous se-
cretion. They reduce the number of tissues and eosinophil
cells. Latest research show that antileukotriene is effective in
the therapy of asthma and easily administered per os. Thera-
peutic effect of these medicines lies in the medication of slight
and moderate forms of bronchial asthma, including other in-
dication (e.g. asthma from the aspirin and reduction of the
corticosteroids dosage) (5).

Effect of the corticosteroids – budesonide (Pulmicort) ap-
plied through inhalation and of antileukotriene – montelu-
kast applied per os at people with bronchial asthma and in-
creased bronchial reactivity was studied in this work. After-
wards, respectively in the end, salbutamol (beta–2-adrenergic
agonist) administered via inhalation as the control and after
all application, measurement of Raw and ITGV conducted,
and SRaw calculated.

2. MATERIAL AND METHODS

Our sample of 12 patients with bronchial asthma and in-
creased bronchial reactivity were subject to examination.
Study included 12 diseased. At least 48 hours prior research
of bronchial reactivity response, patients has not adminis-
tered any of the bronchodilator substances. Examined were
informed regarding manner of the functional pulmonary
tests. Patients were suffering from asthma, with or without
associated bronchitis. Average of the disease period was 8 ± 6
years (from 4-20 years). Average of their age was 35 ± 7 years
(from 29 – 45 years), whereas average of relative weight was
78 ± 7% (from 65 – 72%). The aim of the examination was ex-
plained to each of the patients in advance. Pulmonary func-
tion, composed of measurement of vital capacity (VC), forced
expiratory volume in the first second (FEV1), resistance in the
airways (Raw) and intrathoracic gas volume (ITGV), was de-
finied at the rest.

Overall quantity of the volume of the intrathoracic gas
(ITGV) was measured with the plethysmography method,
including closed gas that do not ventilate. If the residual func-
tional capacity is taken from the ITGV, obtained by the pleth-
ysmography method, we will gain information regarding
quantity of closed gas due to a severe obstruction, cystic
lungs, or pneumothorax. In healthy persons with a normal
pulmonary function, volume of the intrathoracic gas is equal
to the residual functional capacity. From the beta and alpha
glucocorticoids, the ITGV was measured with the pleth-
ysmography method. The performance of measurement of
vital capacity, forced expiratory volume in the first second
(FEV1), resistance in the airways (Raw) and intrathoracic gas
volume (ITGV), was defined at the rest.

SRaw = Raw x ITGV

Raw and the SRaw were taken for analyses. Research of
the bronchial response to different substances was done with
the measurement of Raw and the SRaw as very sensitive in-

Figure 1. Measurement with Body plethysmography: a.
Measurement of parameters of the gas volume in the sternum
(ITGV); registration of flux-volume curve (inspiratory flux and
expiratory flux–L/min); b. Resistance of airways (Raw–L/sec.)
expressed in kPa.
Comparison of Glucocorticoid (Budesonide) and Antileukotriene (Montelukast) Effect

3. RESULTS

Results of this research, in patients with bronchial asthma, indicate that glucocorticoids – budesonide (Pulmicort; 2 x 2 mg inh.) has significant effect (p < 0.01) on reduction of the specific resistance (SRaw) of airways, applied to same patients 3 days after administration of montelukast at home (2 x 10 mg).

Three days after administration of montelukast at home, on the fourth day administered was a capsule to the same patients, and as a result of the blockage of leukotriene receptor (in a dosage of 10 mg per os) significantly (p < 0.05) reduced the increased bronchomotor tonus; same as the effect of the control with Salbutamol (beta2-adrenergic agonist), which is very effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Raw), respectively of the specific resistance (SRaw), (p < 0.01). See fig. 2 and 3.

Table 1. Basic airways characteristics

| n  | Age (y) | Height (cm) | Weight (kg) | VC (%) | FEV1 (%) | Raw (kPa L/s) | ITGV (L)  |
|----|---------|-------------|-------------|--------|----------|--------------|-----------|
| 12 | 35 ± 1.30 | 173.19 ± 1.17 | 76.81 ± 0.78 | 3.19 ± 3.2 | 2.55 ± 3.46 | 0.29 ± 0.01 | 3.66 ± 0.14 |

Figure 2. Effect of glucocorticoids – budesonide (2 inh x 2 mg), and Salbutamol (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 3 days after administration of montelukast at home; (n = 6; X ± SEM).

Figure 3. Effect of montelukast (10 mg tablet – per os), and Salbutamol (2 inh. x 0.2 mg); in Raw, ITGV and SRaw; 3 days after administration of montelukast at home; (n = 6; X ± SEM).

Figure 4. Effect of glucocorticoids – budesonide (2 inh x 2 mg), and Salbutamol to the arterial pressure (AP/systolic/diastolic); 3 days after administration of montelukast at home (2 x 10 mg); (n = 6; X ± SEM).

Figure 5. Effect of montelukast (2 inh x 2 mg), and Salbutamol to the arterial pressure (AP/systolic/diastolic); 3 days after administration of montelukast at home (2 x 10 mg); (n = 6; X ± SEM).
4. DISCUSSION

Systemic glucocorticoids are administered for a long time in treatment of severe chronic asthma or severe acute exacerbations of asthma. Production of forms with aerosol has significantly improved the safety of the treatment with glucocorticoids enabling thus its usage in moderate asthma. Asthmatic patients, in the need for inhalation of β₂ adrenergic agonists four or more times per week, are candidates for inhaled glucocorticoids (6). Although glucocorticoids are very effective in the control of asthma, treatment with systemic glucocorticoids causes considerable side effects. Development of inhaled glucocorticoids, which forward the medicine directly to the inflamed area, is a step ahead in the asthma therapy. These forms increase significantly the therapeutic index of medicine, by lowering very much the number and level of side effects without endangering clinical benefits. Although they change a lot in terms of the affinity to glucocorticoids receptor, namely fluticasone and budesonide have a higher affinity than beclomethasone, these medicine, in proper dosage, are all efficient to control the asthma. Some studies have defined the therapeutic index of various forms of inhaled steroids in treatment of asthma, but in so far data indicate that none of them has any higher therapeutic index (7).

Glucocorticoids act passively in the nerve system by entering to cells, and inducing creation of lipocortin. This protein plays a key role in the inflammatory processes, because it inhibits the phospholipase A2, an enzyme in charge for creation of arachidonic acid—precursor of inflammation mediator (prostaglandin, leukotriene). Mainly administered medicines in asthma are as follows: Pulmicort, Fluticasone, and Budesonide. Corticosteroids (oral, parenteral, or inhalator) reduce the amount of synthesized prostaglandin and leukotriene. Corticosteroids increase the number of beta—adrenergic receptor in leukocyte and increase the response of beta—receptor in the smooth musculature of airways. During the treatment of pneumocystic pneumonia, destroyed organisms release antigens, which cause lung’s inflammatory response, which damages the pulmonary function. Corticosteroids administered orally or intravenously are useful as adjuvant therapy in treatment of severe pneumocystic pneumonia. Concise mechanism of these effects is unknown, but corticosteroids can decrease the subglottic edema by reducing the permeability and capillary dilatation. Corticosteroids administered nasally have local anti-inflammatory effect and minimal systemic effects. Immediate termination of budesonide is generally associated with increase of the bronchial hyperactivity and exacerbations of symptoms, though at 1/3 of patients the symptoms have not aggravated. Patients with a very well controlled disease should undergo a test for termination of inhaled glucocorticoids (4).

In 1990, three new medicines produced, which are used in asthma treatment: Antagonists of leukotriene receptor zafirlukast (8), montelukast (9), and inhibitor of the leukotriene synthesis such zileuton (10).

LTD4 is approximately 1000 times more powerful than histamine in bronchoconstriction. Receptor responsible for the bronchoconstriction effect of leukotriene is sys-LT1 receptor. Although each of cys-LT is agonist to this receptor, LTE4 is less powerful than LTC4 or LTD4. Zafirlukast and montelukast are selective competitive antagonists with high affinity for the receptor cys-LT1 (9).

Zafirlukast is another antagonist of the receptor cys-LT1 administered in some countries in treatment of asthma. Inhibition of cys-LT, which induces the contact of smooth bronchial muscles, included in the therapeutic effects of administration of these agents for relief of asthma symptoms. Effects of cys-LT, born with the bronchial asthma, are not limited only in the contraction of smooth muscles. Cys-LT can increase the micro vascular blood circulation, increase generation of mucous, and appearance of eosinophils and basophils in the airways (11). It is yet unknown how much this inhibition of leukotriene production contributes in the therapeutic effect of these medicines. Maybe, it is worth to mention that zafirlukast inhibits substantially also the manifestation of basophils and lymphocytes in airways after experimental exposure of asthmatic people to an allergen (12).

In clinical trials with zafirlukast, all studies indicated some decrease in the number of asthma exacerbations, with average of reduction to 50% (13). When zafirlukast (14) and montelukast (15) compared with the low dose therapy of inhaled glucocorticoids, improvement in pulmonary function and in the need to reduce the administration of therapy with β₂ adrenergic agonists was higher at patients treated with glucocorticoids. Nonetheless, there was little difference in between subjects treated with steroids and those treated with montelukast in decrease of the number of asthma exacerbations. Clinical trials with antileukotriene medicines were quite heterogeneous in response to the therapy, with patients that can be classified in two groups, those “responding” on the treatment and those “not responding” on it. For patients responding to the treatment with antileukotriene, heart, lungs, and blood institution have recognized these medicines as alternative to inhaled steroids, in small doses, in order to maintain slight chronic asthma under the control.

More studies are needed to define the role of these medicines in moderate and severe asthma. Some clinical trials indicated that leukotriene antagonists have ability to reduce the dose of inhaled steroids, which are necessary to control asthma exacerbations (16). If so, this can be quite important, especially in children suffering from a more severe asthma. Currently, it is impossible to forecast who would benefit more from a provided treatment. This forecast on response generally reflects our limited knowledge on the physiopathology of asthma. Moreover, some components of these changes are possible to explain by many pharmacogenetics factors (17).

Three important mutations found in the promoter region in the gene, which codes 5-lypoxygenases. These mutations bring a small reduction of the promoter activity and synthesis of leukotriene. Around 35% of the population has at least one of these mutations in at least one of the alleles. In clinical trials with placebo seen that individuals with mutation in both alleles responded less to treatment with inhibitors of 5-lypoxygenases than those with two alleles of “wild” type (18).

Zafirlukast and montelukast, antagonists of leukotriene receptor, today are administered in treatment of bronchial asthma. First as addition to other antihistamines, whereas second in prevention of asthmatic attacks. Zileuton is in use, but not found a final place in the therapy. Iralukast is in the stage of preclinical research.

Results of this research in diseased with bronchial asthma,
indicate that glucocorticoid – budesonide (Pulmicort) has significant effect (p < 0.01) in reduction of the specific resistance (Sraw) of airways, applied to same patients 3 days after administration of montelukast at home (2 x 10 mg).

Three days after administration of leukotriene antagonists–montelukast at home, on the fourth day administered was a capsule to the same patients. As a result of the blockage of leukotriene receptor (10 mg per os dose) significantly (p < 0.05) reduced the increased bronchomotor tonus; same as the effect of the control with Salbutamol (beta₂-adrenergic agonist), which is very effective in removal of the increased bronchomotor tonus, causing significant decrease of the resistance (Rraw), respectively of the specific resistance (SRaw), (p < 0.01). Effect of glucocorticoids is more powerful in the obstruction of the creation of the arachidonic acid, of which afterwards released leukotriene with the process of lipoxigenase, and prostaglandin, prostacyclin, and other local chemical mediator, also with very powerful bronchoconstriction effect, are released by cyclooxygenase. Glucocorticoids – budesonide and antagonists of leukotriene in administered doses 3 days after home administration of montelukast at same patients cause decrease of the arterial systolic and diastolic pressure (AP) but not significantly (p > 0.1).

Results of this research in diseased with bronchial asthma, indicate that glucocorticoid – budesonide (Pulmicort) has significant effect (p < 0.01) in reduction of the specific resistance (Sraw) of airways, applied 3 days after administration of montelukast at home in same patients (2 x 10 mg).

Key principles of the asthma therapy have remained unchanged since many decades. Bronchodilator medicines such β₂ agonists of adrenergic receptor with short time of effect are administered immediately to improve the bronchospasm during an asthmatic attack. Anti-inflammatory medicines such inhaled glucocorticoids are administered in relief of the bronchial inflammation aiming reduction of severity and frequency of asthmatic attacks. In hospital admitted patients, often used short courses of systemic steroids.

In patients yet with symptoms, although administered the therapy with inhaled glucocorticoids, to steroid regime can be added agonists of the β₂-adrenergic receptor, for a long period and good results. Once often used, today the methylxanthines are less administered because of the modest effects and small therapeutic window. Selective inhibitors of PDE4, which may have the same efficiency but with less side effects, are being assessed in the clinical trials. Other new agents are aiming to effect on specific mechanisms, which are important in the beginning and progression of asthma. These include antagonists of leukotriene receptor and therapy with anti-IgE,omalizumab. As a conclusion, anti-cholinergic agents such tiotropium approved lately in treatment of the chronic obstructive pulmonary disease.

5. CONCLUSION

Based on gained results, it can be concluded as follows:

Glucocorticoids – budesonide applied via inhalation are more effective in patients with bronchial asthma and increased bronchial reactivity, cause decrease of specific resistance (SRaw) of airways (p < 0.1). Antileukotriene – montelukast administered per os also causes significant decrease of specific resistance (SRaw) of airways (p<0.05). As control – salbutamol, as agonist of beta₂-adrenergic receptor applied via inhalation in patients with bronchial asthma and increased bronchial reactivity, cause also significant decrease of specific resistance (SRaw) of airways (p < 0.01). This suggests that the bronchodilator effect of glucocorticoids is more powerful than the one of antileukotriene, because corticosteroids terminate the early stage of the chemical mediator release (prostaglandin PgD₂, SRS, and leukotriene LTC₄, LTD₄, LTE₄, and cytokinin, etc.) as powerful bronchoconstriction substances, whilst antileukotriene substances have not this feature.