SPECIAL QUESTIONS OF TREATING BRONCHIAL ASTHMA
(RELATIVE THERAPEUTIC INDEX BETWEEN INHALED
FORMOTEROL AND SALBUTAMOL IN ASTHMA PATIENTS,
BRONCHIAL ASTHMA AND THE GASTROESOPHAGEAL
REFLUX)

Ph.D. Theses

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1 INTRODUCTION AND PROBLEM RAISING

Bronchial asthma is one of the most common chronic diseases all over the world. At present, it affects approximately 5% of the population. Yearly, about 15 million disabilities develop because of bronchial asthma that is 1% of the total disabilities. Applying short-acting $\beta_2$ receptor agonists (SABA) as a maintenance therapy, may lead to the development of undesirable side effects. That is how the intention has turned to long-acting $\beta_2$-receptor agonists. The safety and the side effects of $\beta_2$-agonists is an old problem. In connection with this lot of publications forewarn us. The determination of the efficacy and safety is essential. The results of different comparative studies in connection of efficacy and safety between the individual drugs are important. In the practice it is an essential question, how changes the main effect, the bronchodilatation, and the most important side effect, the serum potassium concentration and the cardiovascular parameters by increasing the dose? With regard to this we have only few available data.

In case of using $\beta_2$ receptor agonists in high doses, it may worsen the function of the lower esophageal sphincter, so they may provoke reflux, or it may aggravate the existing reflux.

The gastroesophageal reflux disease (GERD) became one of the most frequent chronic diseases in the last decades of the XX. century. Beside esophageal symptoms, the increasingly extraesophageal (atypical) clinical symptoms are expressly worsening the quality of life nowadays. The chronic dry cough is one of the most common atypical symptom in connection with GERD which is also frequent implicate symptom of asthma. In the group of asthmatic patients high, but particularly different 34-89% prevalence of GERD were reported. Despite of this they rarely thinking on the possibility of reflux by asthmatic patient with chronic cough and the role and importance of the reflex is often controversial.

In the group of asthmatic patients who are coughing chronically and dry, it is an open question that coughing is clearly an asthma symptom or a reflux induced extra-oesophageal GERD manifestation.

2 THE AIMS OF THE STUDY

During my clinical practice, I have met with several coughing, wrongly controlled asthmatic patients requiring rescue preparations frequently. Therefore in my thesis, I deal with two special questions of asthma therapy:

2.1 Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients

We examined the effect and safety of using the special, unique, long-acting $\beta_2$-receptor agonist (LABA) formoterol (Oxis®), as a rescue drug, compared to the traditionally used short-acting $\beta_2$-receptor agonist (SABA) salbutamol (Ventolin®).
Determining one-by-one, between the formoterol (Oxis®) inhaled through turbuhaler and (Ventolin®) inhaled through pMDI,

1. the relative local dose effect, \( \text{max FEV}_1 \)
2. the relative systemic dose effect, \( \text{min SeK}^+ \)
3. the relative therapeutic index, that was determined as the quotient of the relative local dose effect \( \text{max FEV}_1 \) and the relative systemic dose effect \( \text{min SeK}^+ \), while a therapeutic index of a drug can be determined, as the ratio between the strength of desirable and undesirable effects.

2.2 The asthma bronchiale and the gastroesophageal reflux disease
In the group of asthmatic patients who are coughing chronically and dry, the adequate therapy of the concomitant reflux disease, how could change the endpoints of asthma. Does the initiated anti-reflux therapy influence the anti-asthmatic drug requirement?

3 QUESTIONS TO BE ANSWERED

3.1 Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients
1. Is it dose-dependent?
   a. The effect of the local bronchodilator formoterol, in the range of 4.5 µg - 54 µg and salbutamol in the range of 200 µg - 1800 µg?
   b. The systemic \( \text{SeK}^+ \) decreasing effect in formoterol 4.5 µg - 54 µg and salbutamol 200 µg - 1800 µg ranges.
2. Are the changes, measured in cardiovascular parameters (pulse, blood pressure, EKG, QTc), in the normal value?
3. If inhaled formoterol (Oxis®) turbuhaler, and salbutamol (Ventolin®) inhaled through the pMDI, have a better ratio between the local and systemic effect, so their quick attack control and side effect profile is as good, as the traditionally applied salbutamol.

3.2 The asthma bronchiale and the gastroesophageal reflux disease
1. Can GERD be in the background of the chronic coughing of asthmatic patients, treated with anti-asthmatic drugs?
2. Is there a time coincidence between reflux and coughing?
   Within this:
   a.) – does reflux provoke coughing?
   b.) – does coughing provoke reflux?
3. Does simultaneous anti-reflux and anti-asthmatic treatment improve
   a.) the respiratory function parameters?
   b.) the asthma symptom scores?
4. Does the initiated anti-reflux therapy decrease the anti-asthmatic drug requirement?
   a.) the short-acting β₂-agonist requirement?
   b.) the local steroid requirement?

4 SUBJECTS AND METHODS

4.1 Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients

The therapeutic index of a medicine could determine as the rate of the required and unrequired effects, which can serve as a sign of the therapeutic window, or the level of the general usefulness.

In the current study we have determined the correlation between the local and systematic effect of inhaled salbutamol and formoterol in stable asthmatic patients. It is the estimation between the efficiency and safetyness.

4.1.1 Patients

Asthmatic patients were recruited provided they had a normal serum potassium concentration and no history of clinically relevant heart disease, ECG abnormality or hypertension. Eligibility was based on physical examination, vital signs and standard clinical laboratory tests. Asthma was diagnosed according to the American Thoracic Society guidelines. Patients were included only if they could show a stepwise dose-response to salbutamol inhaled via pMDI in the range 100-200 or 100-400 µg, overall by at least 15%. Baseline FEV₁ variability could not be more than ±12% at the enrolment visit and at the study days. Furthermore, baseline FEV₁ was not to increase by more than 15% from one study day to the next.

The 28 asthmatic patients who completed the study were all Caucasian non-smokers (three ex-smokers). Their mean age was 43 (range: 20-64) years and mean weight 72 (range: 49-91) kg. Mean baseline FEV₁ was 2.08 (range:1.46-2.90) L, or 69 (range 49-93)% of predicted normal value. The reversibility after inhalation of salbutamol was 16-82%. All patients showed at least 50% additional reversibility after a cumulative dose of 200 or 400 µg salbutamol compared with a single dose of 100 µg. Twenty-four of 28 patients were on maintainer asthma medication:18 on bronchodilators, and on corticosteroids (not necessary the same patients).

4.1.2 Protocol

The study designed to show dose-response for formoterol both with respect to bronchodilation and serum potassium suppression. Therefore patients were allocated to inhale three single doses of formoterol fumarate dihydrate (4,5, 18 and 54 µg) (Oxis®) via Turbuhaler, two single doses of salbutamol (Ventolin®) (200 and 1800 µg) via pMDI, and placebo in a double-blind, randomized and crossover fashion. The wash-out period between two subsequent treatments was at least 48 h. All active treatments were expected to have a bronchodilating effect, and at least 18 and 54 µg of formoterol and 1800 µg of salbutamol were expected to be serum potassium suppressive. Inspiratory flow via
Turbuhaler and pMDI was monitored by use of a modified Vitalograph® MDI-Compact spirometer. Strenuous activity and intake of beverages containing caffeine or alcohol were not allowed before and during study days. A light breakfast was served before and a light lunch at 4 h after drug administration on study days. Water was allowed „ad libitum”.

Salbutamol 100 µg was to be inhaled regularly at least twice daily via pMDI for 10 days before the first treatment. Thereby, a clinically relevant degree of tolerance to the tested drug was to be ensured. Other regular treatments were kept constant during the study. A follow-up was performed within 2 weeks after the last treatment. FEV₁ and serum potassium were assessed before (-15 min) and at 0.5; 1; 1.5; 2; 3 and 4 h after drug administration. FEV₁ was measured, with the patient sitting in an upright position, using a Vitalograph Alpha spirometer (Vitalograph Ltd., U.K.) Venous blood was drawn via an indwelling catheter into tubes without anticoagulant. After blood coagulation, serum was prepared by centrifugation at 1400 x g and then stored at -20 C grade. An ion selective electrode was used to measure the serum concentration of potassium.

Pulse and blood pressure were checked at -15. min, and at + 0.5.; 1.; 1.5.; 2.; 3.; 4. and 8. h, using standard methods. QT_c (heart rate corrected QT interval, obtained from 12-lead electrocardiograms) were recorded at the -15. min and at the 8. h. Adverse events were also recorded before and 8 h after each administration of study drug and at the follow-up visit. Maximum effects (maximum FEV₁, pulse and systolic blood pressure, and minimum serum potassium concentration and diastolic blood pressure) within 4h after dosing were recorded individually and used in the statistical analysis.

4.1.3 Data analysis
4.1.3.1 Analysis of maximum and minimum values
Analysis of variance models with patients, period, and treatment as factors and the pre-drug administration measurement as covariate were used for the maxima of FEV₁, pulse and systolic blood pressure, and for the minima of serum potassium concentration and diastolic blood pressure.
Missing individual pre-drug administration measurements for serum potassium concentrations were replaced by the within-patient mean value for the other treatments. A multiplicative model was used to analyze maximum FEV₁, whereas an additive model was used for maximum systemic effect. Treatment means were compared pairwise.

4.1.3.2 Estimation of the relative therapeutic index for formoterol and salbutamol
Formoterol and salbutamol were assumed to have similar modes of action – their log-dose response curves were considered to be parallel. “Parallel” in this context means that the curve after administration of, for example, salbutamol could be superimposed by the curve representing formoterol after horizontal translation of the latter. Using the sigmoid model of log-dose response, the difference between formoterol and salbutamol could be explained in terms of a difference in potency. Within the dose range producing 20-80 % of maximum effect, the sigmoid model is well approximated by a linear function. Thus such a linear approximation was used to describe data suggested to be on the linear part
whereas the sigmoid approximation was used to describe data suggested to be partly outside the linear part of the log-dose response curve. A bivariate non-linear mixed-effect model was used to estimate the relative potencies and the relative therapeutic index based on minimum serum potassium and maximum FEV1. The fitted model is presented graphically superimposed on the adjusted mean maximum increase in FEV1 and minimum serum potassium concentration values obtained from the analyses of variance.

4.2 The asthma bronchiale and the gastroesophageal reflux disease

4.2.1 Patients

126 persistent mild or moderate asthmatic patients (49 males, 77 females, mean age: 41.3, range: 14-75 years) with chronic dry cough (continuous coughing for at least three months) were included in the study. Asthma was diagnosed according to the guidelines of the American Thoracic Society at least 12 month before the inclusion in the study. All patients were receiving small or moderate dose of inhaled corticosteroids and used inhaled long-acting β2-agonists as maintenance therapy. Inhaled short-acting β2-agonists were used as rescue medication. All patients were in stable condition in the last 6 weeks preceding the study with no change in their maintenance treatment. Asthmatic patients with negative result on pH monitoring (no pathological reflux detected) were included as controls (n=26).

4.2.2 Protocol

At the visit 0. (screening visit) medical history was taken, physical examination carried out and asthma and GERD symptoms evaluated. Patients satisfying the inclusion criteria were recruited in the study and were given patient diary to record the number of inhaled short acting β2-agonists and return after 14 days for visit 1.

At visit 1 FEV1 and PEF were measured, symptom score was calculated and patients filled a GERD questionnaire. In whom we noticed typical GERD symptoms, we initiated PPI treatment, as a therapeutic test. We performed 24-hour pH monitoring, among those who only had atypical symptoms, and according to the result of this, on the next day they were involved in the GERD or in the CONTROL group. All the patients, involved in the GERD group, received PPI therapy (esomeprazole 40mg/day orally) for 3 months, and we called them back, beside unchanged maintenance anti-asthmatic to the

Visit 2, that was between days 85-95. On visit 2, respiratory function control and the re-evaluation of the GERD questionnaire, symptom scores were performed. We asked the patients not to change their maintenance therapy, and by recording the short-acting β2-agonist requirement, 2 weeks later to present on

Visit 3. If the patient did not require any rescue medication, they were asked to half the dose of their inhaled corticosteroids while continuing with esomeprazole therapy for another 3 months and return

for visit 4. (follow-up visit).
4.2.3 Measurements

4.2.3.1 Lung function test
FEV1 and PEF were measured by means of an electronic spirometer (Medicor MS-11). The best of 3 consecutive manoeuvres was accepted for evaluation. FEV1 and PEF value was expressed as a percentage of the predicted normal value for the subject’s height and age according to European Community for Coal and Steel reference values.

4.2.3.2 24 hour ambulatory pH monitoring
Continuous monitoring of esophageal pH (during which cough and reflux events were recorded) was performed with the pH meter Digitrapper (type: Digitrapper MD, manufacturer: Synectics Medical AB, Stockholm, Sweden) with an antimony nasoesophageal electrode (catheter type: Medtronic Zinetics 24M Internal Reference, manufactured by Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) placed 5 cm above the lower esophageal sphincter.

The evaluated parameters were:
- number of reflux episodes;
- number of reflux episodes longer than 5 minutes;
- longest reflux episode;
- fraction time below pH 4 (total);
- fraction time below pH 4 (supine);
- De Meester score;
- analysis of the temporal association between acid reflux and coughing.

4.2.3.3 Medication
Treatment with proton pump inhibitor, 40 mg esomeprazole orally once daily was performed in patients with typical heartburn and regurgitation as a therapeutic test and also in GERD patients with atypical symptoms only, diagnosed with pH monitoring.

4.2.4 Statistical analysis
Data are expressed as the mean ± SEM. Differences were examined for significance using one sample and two sample t-test. Z-test of a single proportion was used for analysis of the temporal association between acid reflux and coughing. Significance was established at p < 0.05.

5 RESULTS

5.1 Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients
All treatment were well tolerated. No serious adverse event pattern was discernible. Mild, transient tremor was noticed by 2 patients (one patient after F54, the other after S1800). ECG-s were normal; sinus rhythm was always seen. Two patients had extra systoles at the check 8 h after dosing that were not present before dosing (in one patient after F4,5 and S200, and the other after S1800). Normal ECGs were recorded from these patients at subsequent visits.
5.1.1 Describing the data and analysis of the maximal effect
Mean baseline FEV$_1$ was 2.12 (range:2.09-2.14) l, and mean serum K$^+$ concentration was 4.31 (range:4.27-4.34) mmol/l. Bronchodilation was seen after inhalation of formoterol and salbutamol (mean FEV$_1$ at scheduled assessment times are showed in Figure 1.). The absolute increase from pre-drug administration FEV$_1$ was on average 0.33 L after placebo, 0.66-0.82 L after formoterol, and 0.48-0.71 l salbutamol.

The maximum FEV$_1$, observed within 4 h after dosing, was statistically significantly greater after the active treatments compared with placebo: 13, 17, and 20% after F4.5, F18, and F54, respectively, and 7 and 15% after S200 and S1800, respectively. Statistically significantly greater maxima were seen after F54 compared with F4.5 (6%) and after S1800 compared with S200 (9%), showing that bronchodilation was dose dependent within the studied range for both drugs. The maxima after all doses of formoterol were statistically significantly greater than after S200 and so was the maximum after F54 compared with S1800.

![Figure 1. Mean FEV$_1$ values at scheduled assessment times after placebo, formoterol (F) 4.5; 18; and 54 µg; and salbutamol (S) 200 and 1800 µg.](image-url)
Figure 2. Mean serum potassium concentrations at scheduled assessment times after placebo, formoterol (F) 4.5; 18; and 54 µg; and salbutamol (S) 200 and 1800 µg.

The serum potassium concentration was lowered by both formoterol and salbutamol (mean concentrations at scheduled assessment times are given in Figure 2). The minimum concentration, observed within 4 h, was statistically significantly lower than placebo after F18 (-0.29 mmol/l) and F54 (-0.61 mmol/l), and S1800 (-0.30), but not after F4.5 (-0.04 mmol/l) or S200 (-0.07 mmol/l). More individual values below the reference range of serum potassium (3.5-5.0 mmol/l) and statistically significantly lower minima were seen after F54 compared with F18 (-0.32 mmol/l) and after S1800 compared with S200 (-0.23 mmol/l), showing that serum potassium suppression was dose dependent within the studied range. The mean serum potassium minimum values are shown on the 1. Table.

Table 1. Mean maximum or minimum values were:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FEV₁max L</th>
<th>Se-K⁺ min mmol/L</th>
<th>Pulse max beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2,45</td>
<td>4,07</td>
<td>79,8</td>
</tr>
<tr>
<td>Formoterol Turbuhaler 4,5µg</td>
<td>2,78</td>
<td>4,03</td>
<td>83</td>
</tr>
<tr>
<td>Formoterol Turbuhaler 18µg</td>
<td>2,85</td>
<td>3,78</td>
<td>83,2</td>
</tr>
<tr>
<td>Formoterol Turbuhaler 54µg</td>
<td>2,94</td>
<td>3,46</td>
<td>90,5</td>
</tr>
<tr>
<td>Salbutamol pMDI 200µg</td>
<td>2,60</td>
<td>4,00</td>
<td>80,1</td>
</tr>
<tr>
<td>Salbutamol pMDI 1800µg</td>
<td>2,83</td>
<td>3,77</td>
<td>87,1</td>
</tr>
</tbody>
</table>
The mean pre-drug administration measurements for cardiovascular variables were 71-75 bpm (pulse), 126-132 mmHg (systolic blood pressure), 79-82 mmHg (diastolic blood pressure) and 384-394 msec (QTc). Maximum effects seemed to be reached within 4 h after dosing (not shown). The maximum pulse was statistically significantly greater than placebo after F54 (+10.7 bpm) and S1800 (+7.3 bpm) but not after the other treatments. The systolic blood pressure did not increase, but rather unexpectedly seemed to decrease during the first four hours after dosing (not shown). The minimum diastolic blood pressure was statistically significantly lower than placebo after S1800 (-4.9 Hgmm) but not after the other formoterol and salbutamol treatments. The mean QTc at 8. h was statistically significantly longer than placebo after F54 (+17.5 msec) but not after the other treatments.

5.1.2 The evaluation of the relative therapeutic index of formoterol and salbutamol
A log-linear approximation was used to describe the bronchodilatory effect. The corresponding relationship for the two doses of inhaled salbutamol clearly suggested a parallelism with formoterol. Thus a linear approximation with two parallel lines was used to describe the log-dose response curves for maximum FEV1. Parallel straight lines were not considered appropriate for the serum potassium suppressing effects of formoterol and salbutamol (the effect of formoterol 4.5 µg and salbutamol 200 µg, which differed marginally from placebo, seemed to be on the initial flat part of the dose serum potassium suppressing curve). Therefore a sigmoid approximation was more apt to describe the decrease in serum potassium concentration. The fitted model superimposed on mean maximum FEV1 values and minimum serum potassium concentrations obtained from the analyses of variance are showed in Fig. 3.

The model provided good approximations of the means and could therefore be used to estimate relative dose potencies and the relative therapeutic index. The estimated relative dos potencies are indicated in the model as the dose of salbutamol inhaled via pMDI corresponding to formoterol 9 µg inhaled via Turbuhaler.

Formoterol was estimated to be 88 times as potent as salbutamol with regard to suppression of serum potassium and 215 times as potent regarding increase in FEV1. The relative therapeutic index was therefore estimated to be 2.5 (95% confidence interval: 0.9-6.5) in favour of formoterol. The confidence limits for the relative therapeutic index included 1, so the difference between the two drugs was not statistically significant.
**Figure 3.** Mean maximum FEV$_1$ and minimum serum potassium concentration together with approximations of the dose-response relationships. Dashed lines indicate the dose of salbutamol that is equipotent to formoterol 9 µg. The solid line, parallel to the X-axis, indicates the 95% confidence interval for the estimate. Note that relative increase in maximum FEV$_1$ compared to placebo rather than differences are plotted against dose. The reason is that log transformed data were used in the statistical analysis.

### 5.2 The asthma bronchiale and the gastroesophageal reflux disease

#### 5.2.1 Presence of GERD in asthmatic patients with chronic cough

In the 126 recruited patients, GERD was diagnosed in 94 cases, in 31 cases the diagnosis was based on typical GERD symptoms and their cessation due to the therapeutic test, while in the other 63 patients the results of pH monitoring were used to confirm the diagnosis (Table 2.). In patients with GERD, only respiratory symptoms were found in 89 cases while in the other 37 cases both respiratory and gastrointestinal symptoms were present (Fig. 1). Obesity, a known risk factor for GERD, was detected in 66 patients (mean BMI: 37.2).
Table 2. – Data of 24 hr pH monitoring

<table>
<thead>
<tr>
<th>Evaluated parameters</th>
<th>N=89</th>
</tr>
</thead>
<tbody>
<tr>
<td>patient number</td>
<td></td>
</tr>
<tr>
<td>Ph monitoring positive for GERD</td>
<td>N=63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluated parameters</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of reflux episodes</td>
<td>287/24h</td>
</tr>
<tr>
<td>number of reflux episodes longer than 5 minutes</td>
<td>8.9/24h</td>
</tr>
<tr>
<td>longest reflux episode</td>
<td>21.57 min</td>
</tr>
<tr>
<td>fraction time pH below 4 total</td>
<td>18.30%</td>
</tr>
<tr>
<td>fraction time pH below 4 supine</td>
<td>19.70%</td>
</tr>
<tr>
<td>De Meester total score</td>
<td>84.63 ± 18.34</td>
</tr>
</tbody>
</table>

5.2.2 Association between reflux episodes and coughs

We analyzed the temporal association between acid reflux and coughing (Table 3). During the pH monitoring, the 24 hour pH curve was recorded together with cough events. In 403 out of 627 of coughs (64% of all cough episodes), there was a significant association between coughing and acid reflux (p<0.0001). Reflux events preceded coughs in 367 out of 403 events (91%). Cough preceded acid reflux only in 36 out of 403 events (9%).

Table 3. Temporal association between acid reflux and coughing

<table>
<thead>
<tr>
<th>Event</th>
<th>case</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of coughs during the pH monitoring</td>
<td>627</td>
<td>89</td>
</tr>
<tr>
<td>Association between coughing and acid reflux</td>
<td>403/627 (64%)</td>
<td>63</td>
</tr>
<tr>
<td>reflux preceded cough</td>
<td>367/403 (91%)</td>
<td>57</td>
</tr>
<tr>
<td>cough preceded acid reflux</td>
<td>36/403 (9%)</td>
<td>6</td>
</tr>
</tbody>
</table>

Definitions:
- reflux event: pH<4 > 12 sec
- Coughs associated with reflux: -1 or more reflux events during the 5 min. period preceding cough or occurring simultaneously with the cough were observed
  - pH<4 for>=4% of total time and cough improvement to antireflux therapy
- reflux related cough:
- cough related reflux: - cough events during the 5 min. period preceding reflux

Z-test of a single proportion is significant.

5.2.3 Effect of GERD treatment on asthma

All patients diagnosed (either by positive therapeutic test or pH monitoring) with GERD (n=94) received treatment with esomeprazole. No adverse event was observed during the study. After 3 months of esomeprazole treatment, not only GERD and asthma symptoms decreased, but also all other determined outcome measures of asthma improved: FEV1
and PEF values (Table 4), use of rescue medication (Table 5). In the control group (asthmatic patients with chronic cough without GERD), there was no change in symptom scores and FEV1 or PEF values between visit 1 and visit 2 (Table 4). When the changes measured between Visit 1 and Visit 2 were compared between the GERD+asthma and control groups, a significant difference between the changes observed in the two groups was confirmed in FEV1 (p<0.0001) and in PEF (p<0.0001). The frequency distribution of symptom scores demonstrated significant difference before and after therapy in patients with GERD+asthma showing pronounced improvement in symptom scores (Fig. 4) with no change in the control group (Table 5).

The number of rescue medication used after three months of PPI treatment (during the two weeks between Visit 2 and 3) was significantly lower in the group of GERD patients compared to that at baseline (between Visit 0 and 1) (p<0.001), but there was no change in the control group. Thirty nine GERD patients did not require any rescue medication during the 2 week observation period after the 3 months PPI therapy (between Visit 2 and 3) (Table 5). In these patients the dose of inhaled corticosteroid therapy was halved. After an additional 3 months, patients were re-evaluated and only one of them showed worsening in asthma symptoms and lung function, while the rest of them were stable on the combination of PPI treatment and reduced dose of local corticosteroid treatment.

### Table 4. - Lung function test and symptom score before the start and after twelve weeks of PPI therapy

<table>
<thead>
<tr>
<th></th>
<th>before</th>
<th>After</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthmatics with GERD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 %</td>
<td>79.21 ± 0.63</td>
<td>82.92 ± 0.62</td>
<td>p&lt;0.001</td>
<td>94</td>
</tr>
<tr>
<td>PEF %</td>
<td>73.70 ± 0.88</td>
<td>78.42 ± 0.77</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Symptom score (range: 0-10 points)</td>
<td>6.46 ± 0.18</td>
<td>2.00 ± 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group /Asthmatics without GERD</strong></td>
<td></td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>FEV1 %</td>
<td>80.10 ± 0.80</td>
<td>79.82 ± 0.87</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PEF %</td>
<td>78.65 ± 0.88</td>
<td>78.03 ± 0.90</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>symptom score</td>
<td>5.88 ± 0.24</td>
<td>5.57 ± 0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in changes of FEV1 between Asthmatics with GERD and Control group</td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Difference in changes of PEF between Asthmatics with GERD and Control group</td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM. NS= not significant
Table 5. – The number of local short acting beta-2 agonist use of asthmatics with GERD before and after 3 months of PPI treatment and of control group during the two weeks periods

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment Two weeks period</th>
<th>Post-treatment Two weeks period</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of use</td>
<td>Patients requiring treatment</td>
<td>Number of use</td>
<td>Patients requiring treatment</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Asthmatics with GERD</td>
<td>20.24 ± 1.20</td>
<td>94</td>
<td>100</td>
<td>4.56 ± 0.65</td>
</tr>
<tr>
<td>Control group</td>
<td>19.07 ± 1.85</td>
<td>26</td>
<td>100</td>
<td>18.46 ± 1.86</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM. NS= not significant

Fig.4. - The distribution of symptom scores before and after therapy in GERD group
6 CONCLUSIONS

6.1 Relative therapeutic index between inhaled formoterol and salbutamol in asthma patients

Drugs were tolerated well by the patients. The local and systemic effect of both formoterol and salbutamol were dose dependent.

Between the 4.5-54 µg dose of formoterol (Oxis) through Turbuhaler and 200-1800 µg salbutamol (Ventolin) through pMDI, the relative therapeutic index proved to be 2.5, priority of formoterol; so the ratio between the local and systemic effect of formoterol (Oxis), is much favorable, than that of salbutamol pMDI. The clinical significance of this is that the systemic side effect of inhaled formoterol is less significant, than that of equieffective inhaled salbutamol.

6.2 The asthma bronchiale and the gastroesophageal reflux disease

Our examination proved, that in case of persisting, mild or mildly severe, chronically coughing asthmatic patients, if they have no typical reflux symptoms, oesophageal pH monitoring is an effective diagnostic possibility to confirm the reflux disease, as the reason of the symptoms (at least partial). The asthma/GERD connection is a self-inducing process, in that the reflux aggravates asthma that in turn induces further reflux. Simultaneous treatment of the two diseases implies favorable result. Anti-reflux therapy improved not only the GERD symptoms, but also the measures of the outcome of asthma (FEV1 and PEF values, asthmatic symptoms, requirement of rescue drugs).

7 THE MOST IMPORTANT RESULTS OF THE THESIS

1. We showed in our research, that inhaled formoterol (Oxis) is 215 times more effective than the inhaled salbutamol (Ventolin), regarding the local bronchodilator effect, so the FEV1 increase.
2. But inhaled formoterol (Oxis) surpassed the inhaled salbutamol (Ventolin), regarding the systemic effect, the SeK⁺ suppression, only for 88 times.
3. We defined firstly the relative therapeutic index between formoterol and salbutamol at stable asthmatic patients and can be estimated to be 2.5, for the formoterol, so the ratio of its local bronchodilator, rescue and systemic side effects is more favourable, so it is at least as effective and safe.
4. As a rescue drug, the inhaled formoterol is also safe in a higher dose of 54µg, according to this it is useable as a new indication in the treatment.
5. In our examination, we proved that in 75% of chronically coughing asthmatic patients treated with anti-asthmatics, in the background of symptoms there were gastroesophageal reflux.
6. We found significant coincidence in time, between reflux and coughing events: 403/627 (64%) (p<0.0001).
7. In our examination firstly in Hungary we proved that decisively (in 91% of cases), reflux induced the coughing, so we could declare that this is “reflux coughing” which is a special group of the chronic coughing.
8. Only in small ratio (9%) did coughing precede the reflux.
9. Simultaneous snit-asthmatic and increased dose and permanently (for 3 months) applied anti-reflux treatment significantly improved the respiratory function parameters (FEV1, PEF) and the symptom scores.
10. We showed that increased dose anti-reflux therapy decreased the asthma drug requirement. The short-acting β₂ receptor agonist requirement, in the 2-week observation period after the 3-month treatment, in a meaningful extent, significantly (p<0,001) decreased in the GERD asthma group (n=94), and 41.5 % of these patient did not require rescue drug at all. During the further three months PPI therapy, beside decreased dose ICS treatment, from this 39 patients, 38 of them remained 38 stable, well-controlled.

8 PUBLICATIONS

8.1 IMPACT-FACTOR PUBLICATIONS IN THE THEME OF THE THESIS


8.2 PUBLICATIONS PUBLISHED IN HUNGARIAN JOURNAL, IN THE THEME OF THE THESIS


8.3 ABSTRACTS IN CONNECTION WITH THE THEME OF THE THESIS


2. Böcskei Cs, Viczián M, Kozma D. Gastroesophageal reflux disease (GERD) and airway disease. ICACI. XVII. Congress. Sydney, Australia, 14-19 October, 2000.


8. Böcskei Cs, Viczián M, Ajkay Z. (2002) Gastroesophageal reflux disease (GERD) and airway disease. Allergy, 57: suppl. 73,


14. Böcskei Cs, Viczián M, Böszörményi Nagy Gy, Ajkay Z. Gastroesophageal reflux disease (GERD) is one of the common causes of chronic cough. WAO Congress - XVIII ICACI, Vancouver, Canada, September 7-12, 2003. P-13-27.