**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**

**DOCTORAL SCHOOL**

# PhD THESIS

# – ABSTRACT –

## PARTICULARITIES OF BRONCHODILATOR TREATMENT IN ELDERLY PATIENTS WITH BRONCHIAL OBSTRUCTION

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## Introduction

PhD thesis comprises two main parts: the general review concepts known about the elderly pharmacology, age-related changes in respiratory apparatus, particular aspects of the Chronic Obstructive Pulmonary Disease (COPD) in geriatric patients, and an update of concepts related to bronchodilator drugs. The second part of the PhD thesis includes researches about the contributing factors in increasing adherence to bronchodilator therapy and the evaluation of modern bronchodilators in elderly patients with bronchial obstruction.

Keywords: chronic obstructive pulmonary disease, elderly, treatment adherence, modern bronchodilators

### Chapter I. Special pharmacological problems in the elderly

In elderly patients, due to changes in physiological parameters comparing to young adult, pharmacokinetic changes occur and, indirectly, are involved changes in pharmacotoxicological and pharmacotherapeutic response [1].

As a result of different pharmacokinetics in the elderly compared with young adults, there are changes defining the pharmacodynamic parameters: latency, duration, maximum effectiveness, the frequency and intensity of adverse events [2].

### Chapter II. Age-related changes in respiratory apparatus

Ageing produce the enlargement of the terminal respiratory units, decreasing the alveolar air (alveolar area is decreasing with 15% at 70 years old) results in development of "senile emphysema" [3].

Study of healthy people in different ages revealed the reduction of the respiratory muscle strength with age. The decrease in chest wall compliance in the elderly is leading to overstressing the respiratory muscles. Decreased muscle mass in the elderly is associated with decreased perfusion and oxidative activity in muscle. Muscle strength declines by about 2% per year between 20 and 70 years [4].

### Chapter III. Particular aspects of chronic obstructive pulmonary disease (COPD) in elderly patients

COPD is a condition associated with significant morbidity and mortality in the elderly. Age affects the structure, function and respiratory control. Both the lung parenchyma and chest, including respiratory muscles undergo changes affecting respiratory function [5].

Innate and acquired immune imbalance described in the pathogenesis of COPD is a similar process like age-related immunosenescence. Aging and COPD are characterized by the increase of some proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α who are involved in inflammatory diseases related to old age, and is correlated with the degree of COPD obstruction [6].

COPD symptoms in the elderly are non-specific, often difficult to recognize and with late diagnose. The diagnosis of COPD should be based both on the presence of symptoms and spirometric test results [7].

**Chapter IV. Bronchodilator medication**

Bronchodilators are the main treatment of symptoms due to chronic obstruction of the air flow [8].

Bronchodilators, being medication centred by symptoms, is administered as rescue medication in the presence of intermittent symptoms or continuously to prevent and control persistent symptoms [9].

Bronchodilators produce bronchial smooth muscle relaxation. They are classified according to the action mechanism in: adrenomimetics, parasympatholytics and musculotrope agents and they can be used as single therapy or in combination [2].

Inhaled route is preferred because it gives bronchial-selectivity and the advantage of high efficiency at lower doses, better tolerated and reduced systemic side effects compared with the other routes of administration (oral or injectable). Inhaler devices, metered-dose inhalers (MDI) or dry-powder inhalers (DPI) must be properly handled. Therapeutic benefit depends on adequate airway drug deposition. Inhaler technique is crucial, but disappointingly, this is sub-optimum particularly in the elderly [9].

An important role in the management of COPD can be obtained with a single daily-dose regimen, thus ensuring increased patient adherence to treatment and the improvement in quality of life. Indacaterol, olodaterol or vilanterol are ultra-long acting beta-2 adrenomimetics with a single administration in COPD patients.

**PERSONAL RESEARCH**

**Chapter V. Inhaled treatment and medication adherence in elderly patients with obstructive bronchial disease**

**Introduction**

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, with prevalence in patients over 40 years, estimated between 5% and 16%, depending on the country [10].

A diagnosis of COPD should be considered in all patients with a history of exposure to cigarette smoke or occupational factors pollutants chronic cough, sputum or dyspnea [11]. Dyspnea in elderly patients can be attributed to other co-morbidities such as congestive heart failure, hypertension and certain neurological or physiological symptoms related to old age [12].

Pulmonary function tests (PFT) is the gold standard in the diagnosis of COPD. Decreasing of lung volumes with age, even in individuals without respiratory disease, is leading to a difficult interpretation of PFT in elderly.

**Objectives**

The aim of this study was to identify the factors that contribute to increasing adherence to inhaled medication and to demonstrate the correlation between these factors, the pulmonary function and the quality of life, through COPD assessment test (CAT) in elderly patients with stable COPD.

**Materials and methods**

We studied a group of 36 patients with confirmed COPD diagnosis admitted to the Medical Clinic II, Clinical Municipal Hospital "Filantropia" Craiova between September 2011 and September 2012. Inclusion criteria: (1) age over 65 years; (2) patients with previously confirmed diagnosis of COPD; (3) current status of the smoker, ex-smoker or non-smoker; (4) patients able to perform valid spirometry; (5) bronchodilator therapy was initiated at least 12 months before inclusion, using beta-2 agonist, a muscarinic antagonist, inhaled corticosteroid without any change of the therapy in the past 3 months.

The study enrolled 11 female and 25 male, 31 current smokers or former smokers, using inhaled therapy for at least 12 months.

The patients were using the dry powder inhalation device (DPI) Turbuhaler (long-acting beta-2 agonist with corticosteroid – budesonide/ formoterol), Diskus (long-acting beta-2 agonist with corticosteroid – fluticasone/salmeterol) or HandiHaler (long-acting muscarinic antagonist - Tiotropium) and MDI device with short-acting beta-2 agonist (Salbutamol) as rescue medication.

19 of the 36 patients (52.7%) were provided instruction on inhalation technique and how to use the inhalers. All 19 patients had their inhalation skills tested and were instructed to inhale correctly depending on the specific characteristics of each device. They were given both verbal instructions and demonstrations of inhalation technique. No patients received written instructions.

**Statistical analysis**

All data were analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and the IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA).

**Results**

- **Adherence to inhalation therapy score**

**Table 1:** evaluation after 8 weeks

| | | Total | Adherence | |
|---|---|---|---|---|
| | | | Good | Poor |
| Number of patients | | 36 | 19 | 17 |
| Age (years) | | 71 | 72 | 69 |
| Gender (male) | | 25 | 15 | 10 |
| Current smokers | | 6 | 5 | 1 |
| Period of inhaler use (years) | | 3 | 3 | 3 |
| Frequency of inhaler use (per day) | | 2.36±1.02 | 2.53±1.07 | 2.18±0.95 |
| Type of inhaler device | DPI | 13 | 7 | 6 |
| | MDI | 11 | 6 | 5 |
| | DPI + MDI | 12 | 6 | 6 |
| Presence of inhalation instruction | | 19 | 14 | 5 |
| GOLD stage | I | 9 | 4 | 5 |
| | II | 20 | 11 | 9 |
| | III | 5 | 3 | 2 |
| | IV | 2 | 1 | 1 |
| CAT score at baseline | | 16.94±6.11 | 17.74±6.33 | 16.06±5.92 |
| CAT score after instruction | | 15.86±5.85 | 15.47±5.70 | 16.29±6.16 |
| FEV1 % predicted value – baseline | | 61.64±13.03 | 59.95±12.86 | 63.53±13.35 |
| FEV1 % predicted value – final | | 62.92±13.05 | 62.32±12.91 | 63.59±13.58 |
| FEV1/FVC % – baseline | | 59.89±6.16 | 59.63±6.54 | 60.18±5.90 |
| FEV1/FVC % - final | | 60.61 ± 6.01 | 60.68±6.33 | 60.53±5.81 |
| Overall adherence score | | 3.99±0.70 | 4.61± 0.30 | 3.31± 0.19 |

The average adhesion score was 3.99 (**Table 1**). 19 from 36 patients, (52.7%) were showed good adherence to inhaled therapy (score at least 4),

while 17 patients (47.3%) showed different levels of poor adherence to treatment (with a score less than 4).

There is a strong link between training patients and their adherence to treatment, over 70% of patients receiving instructions were considered with high adherence, and just under 30% of the untrained proving inhaler adherence (p Fisher test = 0.0095 <0.05) . This is supported by the result calculated by odds ratio, OR = 6.72 (95% confidence interval = 1.56 to 28.93 - statistically significant. The probability for a patient receiving inhalation instructions to be adherent is 6.72 times higher than an untrained patient.

- **Improving pulmonary function by adhering to treatment**

Improving adherence to inhaled therapy increased the mean values of FEV1 in group adherent than two percent.

- **Evolution of CAT scores based on adherence to treatment**

Initially, the group of adherent patients had a CAT score a little higher compared to non-adherent patients, but in the end, the patients with adherent profile recorded CAT scores lower than others.

**Discussion**

COPD is a progressive and irreversible disease, with an annual decline of FEV1 which is depending on the exacerbation rates, on smoking cessation and appropriate adherence to treatment. Asukai (2013), designing a predictive model which states that patients with treatment disruptions will have FEV1 values lower or similar to those patients not receiving any inhaled therapy [13].

Analyzing the data of 4951 patients from 28 countries, Jones et al state that a correct treatment of COPD significantly improves quality of life assessed by all the three scores of the St George questionnaire in: symptoms, activity and impact. Quality of life is rapidly deteriorating in patients in GOLD stages III and IV than in those in stage II [14].

In a 2011 study were analyzed the responses of 1817 patients in the 8 CAT domains and the scores showed that the average health impairment is related to the severity of the obstruction and each GOLD stage is correlated with a CAT score (stage I: 16.2 ± 8.8, stage II: 16.3 ± 7.9, stage III: 19.3 ± 8.2, stage IV: 22.3 ± 8.7). The scores were significantly better in patients with stable disease (17.2 ± 8.3) than in patients with current exacerbation (21.3 ± 8.4) [19]. CAT score and FEV1 are complementary both in assessment and management of COPD and to evaluate response to treatment and progression of the disease.

**Conclusions**

1 Our research demonstrates the link between receiving inhaler instructions, adherence to inhalation treatment and quality of life in elderly COPD patients.

2 Identification and management of the factors related to adherence to treatment improve the health status of COPD patients.

3 There is a strong link between training patients and their adherence to treatment, over 70% of patients showing good adhesion after training, while less than 30% of the untrained proving treatment adherence.

4. In adherent patients, we found a highly significant improvement in FEV1 values between initial and final, demonstrating the importance of adherence to treatment.

5. An improvement by more than 2 units CAT score in adherent patients proves to be highly statistically significant, showing that patients with adherence to treatment have an improved quality of life.

6. Acquiring a correct inhalation technique increases adherence to inhaled therapy, significantly improving the quality of life in elderly COPD patients.

## Chapter VI. Efficacy of modern long-acting bronchodilators in elderly patients with Chronic Obstructive Pulmonary Disease

**Introduction**

Inhaled bronchodilator therapy is the mainstay of the treatment in the management of COPD [15]. Only for the stage I COPD patients, with mild symptoms and low risk of exacerbation, it is recommended treatment with a short-acting bronchodilator [16]. The current Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommends the use of long-acting bronchodilators as first-line maintenance treatment for moderate to severe COPD [17].

Currently there are available two classes of long-acting inhaled bronchodilators: long-acting β2-agonists and long-acting muscarinic antagonists. While the β2-agonists directly induce bronchodilation causing the relaxation of airway smooth muscle by stimulating the β2-adrenoceptor, muscarinic antagonists prevent bronchoconstriction by competitive antagonism to muscarinic receptors [18].

Because of the central role of long-acting bronchodilators in the treatment of COPD, it is increasing the interest of researchers for the development of new bronchodilators agents administered in a single dose to simplify the regimen for the patients with moderate to severe COPD in order to increase patient adherence to treatment.

Indacaterol is the first ultra-long acting β2-agonist that has a 24-hour bronchodilator effect, administered in a single daily dose [19]. It is recently introduced in Romania, and his comparison with tiotropium, a well known long-acting bronchodilator, can show exactly the place of indacaterol in the current treatment of COPD, especially in elderly patients.

**Objectives**

The objective of the study was to evaluate the effectiveness of modern bronchodilators in once-daily administration on pulmonary function tests, dyspnea scale, BODE index and the need to use rescue medication in elderly patients with COPD.

*Subjects*

The patients included in the study were admitted in the Medical Clinic II, Clinical Municipal Hospital „Filantropia" Craiova over the period May 2013 -July 2014. The study included 24 patients over the age of 65 (16 males, 8 females) previously diagnosed with moderate and severe COPD with a baseline medication with tiotropium 18 μg once daily (8 patients), with combination budesonide and formoterol 320/9 μg twice daily (11 patients) or with combination fluticasone and salmeterol 500/50 μg twice daily (5 patients).

**Table 2**: Baseline characteristics of the subjects

| | |
|---|---|
| Number | 24 |
| Age – years | 72.91 ± 6.57 |
| Sex: male/female | 16/8 |
| BMI $kg/m^2$ | 28.33±5.00 |
| Smokers/ex-smokers | 19 |
| Severity of airflow limitation<br>Moderate<br>Severe | <br>15<br>9 |
| Baseline medication<br>Tiotropium<br>Budesonide-Formoterol<br>Fluticasone-Slameterol | <br>8<br>11<br>5 |
| FEV1 % | 52.5±9.81 |
| FEV1/FVC % | 57.92±6.98 |
| $SpO_2$ | 95.5±2.04 |
| mMRC scale | 2.375±0.65 |
| BODE Index | 4.46±1.96 |
| Rescue medication | 1.67±1.13 |

Subjects were over 65 years old with no exacerbation during the 3 month prior to the study, with a body-mass index (BMI) of 28.33±5.00, 19 smokers/ex-smokers, 15 patients in stage II GOLD, and 9 patients in stage III GOLD, with a mean oxigen saturation ($SpO_2$) of 95.5%±2.04, a modified Medical Research Council (mMRC) dyspnea scale of 2.375±0.65 and a BODE index score of 4.46±1.96, with a rescue medication of 1.67±1.13 salbutamol doses daily (Table 2).

*Study design*

After the baseline evaluation, patients were divided into 3 groups: 8 patients already receiving tiotropium became the control group (group 3). The other 16 patients were randomly divided into 2 groups each with 8 patients: the group 1 received new treatment with indacaterol 150 µg once-daily using Breezhaler inhalation device (group indacaterol) and the group 2 received new treatment with tiotropium 18 µg once-daily using HandiHaler inhalation device (group tiotropium). The 3 groups were reassessed after 60 days. All subjects visited the hospital in the morning, performed a spirometry and a baseline digital oximetry, answered the mMRC questionnaire and performed a 6 minutes walk test (6MWT) conducted in a 30 m corridor useful to calculate the BODE index (6MWT, FEV1 % predicted, mMRC dyspnea score and BMI).

**Statistical analysis**

Data are summarized as the mean ± standard deviation. P-value less than 0.05 were considered significant. Statistical differences before and after the treatment with long-acting bronchodilators were assessed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and the IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY , USA).

**Results**

- *Characteristics of group I (indacaterol) patients after 60 days of treatment*

After 60 days indacaterol treatment were noted significant improvement in FEV1 from 52.375±5.63 to 55.25±6.63 (p Wilcoxon = 0.016 <0.05), significant appreciation of the report FEV1/FVC from 59.50±5.21 to 60.75±5.70 (p Wilcoxon = 0.037 <0.05), SpO2 appreciation from 94.875±1.46 to 96.25±0.89 (p Wilcoxon = 0.022 <0.05), the mMRC dyspnea score improves to 2.375±0.52 from 2.625±0.52 even if it is statistically insignificant (p Wilcoxon = 0.187> 0.05), BODE index significantly improves from 4.75±1.04 to 3.75±1.04 (p Wilcoxon = 0.021 <0.05) and the number of salbutamol doses rescue medication decrease

from 1.25±1.04 to 0.625±0.74 although not significant (Wilcoxon p = 0.057 <0.05). It is found an improvement of all the parameters in elderly COPD patients receiving treatment with indacaterol instead of a combination with long-acting β2-agonist and inhaled corticosteroid (Table 3).

**Table 3:** Characteristics of group I (indacaterol) patients at baseline and after 60 days of treatment

| Characteristics | Baseline | After Indacaterol | p-value |
|---|---|---|---|
| Patients | 8 | | |
| Age-years | 74.625±4.78 | | |
| Sex: male/female | 6/2 | | |
| BMI kg/$m^2$ | 31.37±3.96 | | |
| Severity of airflow limitation<br>Moderate<br>Severe | <br><br>5<br>3 | | |
| Previous medication<br>Budesonid-Formoterol<br>Fluticasone-Salmeterol | <br>4<br>4 | | |
| FEV1 % | 52.375±5.63 | 55.25±6.63 | 0.016 |
| FEV1/FVC % | 59.50±5.21 | 60.75±5.70 | 0.037 |
| $SpO_2$ % | 94.875±1.46 | 96.25±0.89 | 0.022 |
| mMRC scale | 2.625±0.52 | 2.375±0.52 | 0.187 |
| BODE index | 4.75±1.04 | 3.75±1.04 | 0.021 |
| Rescue medication | 1.25±1.04 | 0.625±0.74 | 0.057 |

- *Characteristics of group II (tiotropium) patients after 60 days of treatment*

After 60 days of treatment with tiotropium was noted: significant improvement of the FEV1 values from 50.75±9.53 to 53.125±8.13 (p Wilcoxon = 0.029 < 0.05), insignificant appreciation of the report FEV1/FVC from 56.5±9.47 to 57.75 ± 8.28% (Wilcoxon p = 0.136 > 0.05), significant appreciation of $SpO_2$ from 95.875±2.03 to 96.75±1.49 (p Wilcoxon = 0.036 < 0.05), the mMRC dyspnea score improves from 2.375±0.74 to 2.25±0.71 even if insignificant (p Wilcoxon = 0.382 > 0.05), significantly improve in BODE index from 4.625±2.13 to 4.00±1.77 (p Wilcoxon = 0.031 <0.05), and significantly decrease in the need doses of salbutamol as rescue medication from 2.00±1.07 to 1.00 ± 0.93 (p Wilcoxon = 0.021 <0.05). It is found to improve the monitoring of all the

parameters in elderly COPD patients who have received treatment with inhaled cholinergic antagonist with long duration of action (tiotropium), and administered in a single daily dose combinations where beta-2 agonist with a long duration action and inhaled corticosteroid (Table 4).

**Table 4:** Characteristics of group II (tiotropium) patients at baseline and after 60 days of treatment

| Characteristics | Baseline | After Tiotropium | p-value |
|---|---|---|---|
| Patients | 8 | | |
| Age-years | 73.125±7.39 | | |
| Sex: male/female | 5/3 | | |
| BMI kg/$m^2$ | 27.125±4.85 | | |
| Severity of airflow limitation<br>Moderate<br>Severe | <br><br>5<br>3 | | |
| Previous medication<br>Budesonid-Formoterol<br>Fluticasone-Salmeterol | <br>7<br>1 | | |
| FEV1 % | 50.75±9.53 | 53.125±8.13 | 0.029 |
| FEV1/FVC % | 56.5±9.47 | 57.75±8.28 | 0.136 |
| $SpO_2$ % | 95.875±2.03 | 96.75±1.49 | 0.036 |
| mMRC scale | 2.375±0.74 | 2.25±0.71 | 0.382 |
| BODE index | 4.625±2.13 | 4.00±1.77 | 0.031 |
| Rescue medication | 2.00±1.07 | 1.00±0.93 | 0.021 |

**Discussion**

For the group I (indacaterol) patients we noticed a significant difference (p Wilcoxon = 0.016 <0.05) between the initial and final FEV1 measurements. Most patients with COPD, especially those who continue to smoke, suffer an accelerated decline in lung function compared to individuals without airflow limitation. Because of the easy way of measuring, and the reproducibility, the FEV1 parameter is used to assess the decline in lung function, and to monitor the proper management of patients with COPD [20]. In a 52-week randomized study, on 366 patients receiving 150 μg or 300 μg indacaterol once daily, had a significant improvement in FEV1 (170 ml), significantly higher compared to the placebo [21]. Another study, conducted on 90 patients receiving 300 μg

indacaterol once daily for 3 weeks demonstrated an increase in FEV1 (250 ml) highly significant compared to placebo [22].

For the group II patients (tiotropium) we found significant improvement (Wilcoxon $p = 0.029 < 0.05$) in FEV1 values after 60 days of treatment. A study of 311 patients with COPD, smokers treated with tiotropium 18 μg or placebo, with mean values of FEV1 of 1.11 l (tiotropium group) and 1.13 l (placebo group) demonstrated, after 12 weeks of treatment, the average FEV1 in tiotropium patients increased significantly by 102 ml, compared to placebo. Moreover, in the current smokers mean FEV1 increased by 138 ml and in ex-smokers with only 66 ml, suggesting that tiotropium improves lung function regardless of smoking status [23]. In a study of 244 moderate COPD patients treated 12 weeks with tiotropium or placebo, there were obtained the average increase of 166 ml of FEV1 values for tiotropium group compared with placebo group, with similar occurrence of adverse effects [24].

**Conclusions**

1. Advanced age is a significant predictor factor for poor adherence to pharmacological therapy due to the complexity of the regimen coupled with memory loss and cognitive impairment.

2. Currently there are two classes of long-acting inhaled bronchodilators: β2-agonists who induce directly bronchodilation, causing relaxation of airway smooth muscle by stimulating the β2-adrenoceptors and muscarinic antagonists which prevent bronchoconstriction by competitive antagonism at the muscarinic receptors.

3. Bronchodilator therapy in COPD seeks to improve the quality of life, increase exercise tolerance, improve lung function and prevent exacerbations. In recent years there is growing interest in the use of bronchodilator agents administered in a single-daily dose in order to simplify treatment and increase adherence to treatment of patients with moderate to severe COPD.

4. Indacaterol is the first β2-agonist with ultra-long acting formulation that has a 24-hour bronchodilator effect, administered in a single daily dose. Tiotropium is a muscarinic receptor antagonist comprising a quaternary ammonium associated with low systemic absorption, with a long duration of action and without penetrating the blood-brain barrier.

5. We noticed an improvement of all the monitoring parameters in elderly patients with COPD who received indacaterol rather the combinations of β2-agonist and long-acting inhaled corticosteroid: significant difference between initial and final values of FEV1; significant

difference between the values of FEV1/FVC between baseline and final; significant difference between initial and final SpO2; mMRC values have improved, but not significantly; significant difference between initial and final values of BODE index score; significant decrease in the number of daily rescue medication use.

6. There is an improvement of all the monitoring parameters in elderly patients with COPD who received tiotropium instead combinations of β2-agonist and long-acting inhaled corticosteroid: significant difference between baseline and final values of FEV1; 1% improvement in the values of FEV1/FVC; significant difference between initial and final SpO2; mMRC values have increased slightly; significant difference between initial and final values of BODE index; significant decrease in the number of daily rescue medication doses.

7. There were no noteworthy changes in monitoring parameters of the control group patients.

8 In our study we can say that by using long-acting bronchodilators, administered in a single daily dose, we achieved significant improvement in the lung function, amelioration of exercise tolerance and improve quality of life in elderly patients with COPD.

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