ORIGINAL ARTICLE

EFFICACY OF INDACATEROL, A MODERN ULTRALONG-ACTING BRONCHODILATOR, IN ELDERLY PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent chronic diseases among elderly population worldwide. Because of the central role of long-acting bronchodilators in the treatment of COPD, the interest of researchers for the development of new bronchodilators agents administered in a single dose is increasing in order to simplify the regimen for patients with moderate to severe COPD and to improve patient adherence to treatment.
The objective of this study was to evaluate the effectiveness of modern bronchodilators in once-daily administration on pulmonary function tests, dyspnoea scale, BODE index and the need to use rescue medication in elderly patients with COPD.
The study was performed on patients aged over 65 years old previously diagnosed with moderate and severe COPD having a baseline medication with tiotropium, combination of budesonide and formoterol or combination fluticasone and salmeterol. After a baseline evaluation of the parameters mentioned above, the patients were divided into three groups. Patients already receiving tiotropium became the control group ant the others were randomly divided into two groups: one receiving treatment with indacaterol and the other new treatment with tiotropium. All the patients were reassessed after 60 days.
We noticed an improvement of all parameters selected in patients who received indacaterol and tiotropium: a significant difference between baseline and final values of forces expiratory volume in 1 second (FEV1), report between forced expiratory volume and forced vital capacity (FEV1/FVC), and peripheral capillary oxygen saturation (SpO_2) and also a significant decrease of the BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) index score and the number of daily rescue medication use at the end of the study.

Rezumat

Boala pulmonară obstructivă cronică (BPOC) este una dintre cele mai frecvente boli cronice care apar la pacienţii vârstnici. Datorită rolului central pe care bronhodilatatoarele cu durată lungă de acţiune îl au în tratamentul BPOC, interesul cercetătorilor pentru dezvoltarea de noi agenţi bronhodilatatori cu administrare în doză unică este crescut cu scopul de a simplifica regimul de administrare la pacienţii cu BPOC moderată şi severă şi de a îmbunătăţi aderenţa pacienţilor la tratament.
Obiectivul studiului a fost evaluarea eficienţei bronhodilatatoarelor moderne, cu o singură administrare pe zi, asupra funcţiei pulmonare, a scalei dispneei, a indexului BODE şi a numărului necesar de doze zilnice de medicaţie de urgenţă.
Studiul a inclus pacienţi peste 65 de ani diagnosticaţi cu BPOC trataţi în prealabil cu tiotropium, combinaţia budesonid-formoterol şi combinaţia fluticazonă-salmeterol.
După evaluarea iniţială a parametrilor menţionaţi anterior, pacienţii au fost repartizaţi în trei grupuri. Pacienţii trataţi deja cu tiotropium au reprezentat grupul martor, iar ceilalţi pacienţi au fost repartizaţi aleator în două grupuri: grupul 1 a primit tratament cu indacaterol, iar grupul al 2-lea tratament *de novo* cu tiopropium. Toţi pacienţii au fost reevaluaţi după 60 de zile.
Am observat ameliorarea tuturor parametrilor selectaţi la pacienţii vârstnici cu BPOC care au primit tratament *de novo* cu indacaterol şi tiotropium: o diferenţă semnificativă între valorile iniţiale şi finale ale VEMS, raportului VEMS/CVF şi SpO_2, precum şi scăderea semnificativă a scorului indexului BODE şi a numărului necesar de doze zilnice de medicaţie de urgenţă la finalul studiului.

Keywords: Chronic obstructive pulmonary disease (COPD), elderly patients, indacaterol, tiotropium

Introduction

Ageing is commonly characterized as a progressive impairment of function, resulting in an increased vulnerability to environmental challenge and a growing risk of disease [2]. Chronic obstructive pulmonary disease (COPD) is one of the most prevalent chronic diseases among elderly population worldwide.

Inhaled bronchodilator therapy is the mainstay of the treatment in the management of COPD [18]. Only for the stage I COPD patients, with mild symptoms and low risk of exacerbation, it is recommended the treatment with a short-acting bronchodilator. The current guidelines of Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend the use of long-acting bronchodilators as first-line maintenance treatment for moderate to severe COPD [8].

Currently there are available two classes of long-acting inhaled bronchodilators: long-acting β2-agonists and long-acting muscarinic antagonists. While the long-acting β2-agonists directly induce bronchodilatation causing the relaxation of airway smooth muscle by stimulating the β2-adrenoceptor, long-acting muscarinic antagonists prevent bronchoconstriction by competitive antagonism to muscarinic receptors [4].

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

Indacaterol is the first β2-agonist with ultralong-acting formulation that has a 24-hour bronchodilator effect, administered in a single daily dose [6]. 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 for elderly patients.

Pharmacological profile of indacaterol. Indacaterol demonstrates a rapid onset of action and a bronchodilatation that last for 24 h. Studies with isolated human bronchi and small-airway lung slices demonstrate an onset of action similar to formoterol and salbutamol, but faster than salmeterol and a significantly longer duration of action than formoterol and salmeterol [17].

The chemical structure of indacaterol is 5,6-diethyl substituted indan analogue, (R)-5-{2-[(5,6-diethyl-2,3-dihydro-1H-inden-2-yl)amino]-1-hydroxyethyl}-8-hydroxyquinolin-2(1H)-one [1] (Figure 1).

The faster onset of action and the longer effect of indacaterol may be related to its interaction with lipid bilayers [12]. Indacaterol and salmeterol show minor differences in their steady-state and kinetic interactions with lipid membranes. Indacaterol shows higher partitioning into the micro-environment of the receptor and a faster membrane permeation that contribute to its faster onset and his longer duration of therapeutic action. In contrast to salmeterol, indacaterol does not alter membrane fluidity, obtaining an increased intrinsic efficacy. It has been suggested that lipid rafts, areas of cell membranes in which β2-adrenoreceptors are held together in close contact with signalling molecules and effectors, and calveolae, a special type of lipid rafts, small invaginations of the plasma membrane in airway smooth muscle, might play a role in the long duration of indacaterol [5]. It appears that indacaterol has a twofold higher affinity for this lipid rafts than salmeterol, which may contribute to its longer duration of action [21].

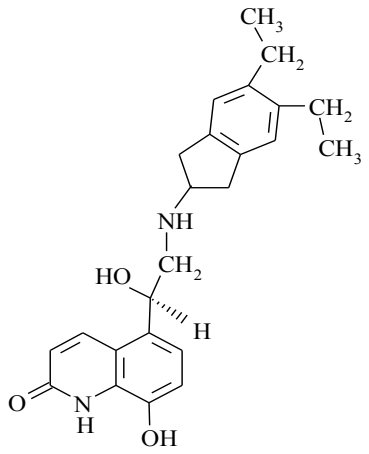

Figure 1.
The chemical structure of indacaterol

The objective of this study was to evaluate the effectiveness of modern bronchodilators in once-daily administration on pulmonary function tests - forced expiratory volume in 1 second (FEV1 %), forced vital capacity (FVC %), peripheral capillary oxygen saturation (SpO_2 %), modified Medical Research Council (mMRC) dyspnoea scale, BODE index (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) and the need to use rescue medication in elderly COPD patients.

Materials and Methods

Patients. The patients included in the study were admitted in the 2nd Medical Clinic of the Clinical Hospital „Filantropia" Craiova between May 2013 and July 2014. The study was approved by the Ethical Commission of the Hospital.

The study was performed on 24 patients (16 males and 8 females) previously diagnosed with moderate and severe COPD having a baseline medication with tiotropium 18 μg once daily (8 patients), the combination budesonide and formoterol 320/9 μg twice daily (11 patients) or with combination fluticasone and salmeterol 500/50 μg twice daily (5 patients). Inclusion criteria: subjects over 65 years old with no exacerbation during the last three months prior to the study, able to perform valid spirometry and the six minutes' walk test, with a body-mass index (BMI) of 28.33±5.00. Patients were excluded from the study if they had asthma

history, concomitant pulmonary or cardiovascular diseases. 19 patients were smokers/ex-smokers, 15 patients were in stage II GOLD (moderate – FEV1 between 50-80 % of predicted) and 9 patients in stage III GOLD (severe – FEV1 between 30-50 % of predicted), with a SpO_2 of 95.5 ± 2.04 %, mMRC dyspnoea scale of 2.375±0.65, BODE index score of 4.46 ± 1.96 and the need of rescue medication of 1.67 ± 1.13 salbutamol doses daily (Table I).

Table I

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 Moderate Severe	 15 9
Baseline medication Tiotropium Budesonide-Formoterol Fluticasone-Salmeterol	 8 11 5
FEV1%	52.5 ± 9.81
FEV1/FVC %	57.92 ± 6.98
SpO_2%	95.5 ± 2.04
mMRC dyspnoea scale	2.375 ± 0.65
BODE Index	4.46 ± 1.96
Rescue medication	1.67 ± 1.13

Abbreviations: BMI: body-mass index; FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity; SpO_2: peripheral capillary oxygen saturation; mMRC: modified Medical Research Council; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity.

Study design. After the baseline evaluation, patients were divided into 3 groups: 16 patients were randomly divided into two groups of eight patients each: patients from the 1st group received new treatment with indacaterol 150 µg once-daily using Breezhaler inhalation device and the 2nd group received new treatment with tiotropium 18 µg once-daily using HandiHaler inhalation device; the other eight patients already receiving tiotropium became the control group (3rd group). The patients were reassessed after 60 days. All subjects visited the hospital in the morning, performed a spirometry (using a Cardio-Touch-SPM-300 spirometer) and a baseline digital oximetry (using a WK-200 digital oximeter), answered the mMRC questionnaire and performed a 6 minutes' walk test (6 MWT) conducted in a 30 m corridor useful to calculate the BODE index (6 MWT, FEV1 % predicted, mMRC dyspnoea score and BMI). BODE index includes several useful parameters for the overall evaluation of COPD: symptoms, nutritional status, exercise capacity and lung function by spirometry. BODE index score range is between zero (0) and ten (10) points, and the higher is the score, the higher is the risk of death.

Statistical analysis. Data are summarized as the mean ± standard deviation. p-value less than 0.05 were considered significant. Statistical differences before and after 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 and Discussion

Characteristics of the patients from the 1st group after 60 days of treatment. After 60 days of indacaterol treatment were noted significant improvement in FEV1% from 52.375 ± 5.63 to 55.25 ± 6.63 (p Wilcoxon = 0.016 < 0.05) and of FEV1/FVC ratio from 59.50 ± 5.21 to 60.75 ± 5.70 (p Wilcoxon = 0.037 < 0.05); appreciation of SpO_2% from 94.875 ± 1.46 to 96.25 ± 0.89 (p Wilcoxon = 0.022 < 0.05); the mMRC dyspnoea score improves from 2.625 ± 0.52 to 2.375 ± 0.52 even if it was 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 decreases from 1.25 ± 1.04 to 0.625 ± 0.74 although not significant (p Wilcoxon = 0.057 < 0.05) (Table II).

Table II

Characteristics of the patients from the 1st group during the study

Characteristics	Baseline	After 60 days of treatment with 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 Moderate Severe	 5 3		
Previous medication Budesonid-Formoterol Fluticasone-Salmeterol	 4 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 dyspnoea 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

Abbreviations: BMI: body-mass index; FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity; SpO_2: peripheral capillary oxygen saturation; mMRC: modified Medical Research Council; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity.

Characteristics of the patients from the 2nd group after 60 days of treatment. After 60 days of treatment with tiotropium we noted a significant improvement of the FEV1 % values from 50.75 ± 9.53 to 53.125 ± 8.13 (p Wilcoxon = 0.029 < 0.05) and insignificant appreciation of the FEV1/FVC ratio from 56.5 ± 9.47 to 57.75 ± 8.28 % (p Wilcoxon = 0.136 > 0.05); a significant improvement of SpO_2 % from 95.875 ± 2.03 to 96.75 ± 1.49 (p Wilcoxon = 0.036 < 0.05); mMRC dyspnoea score improves from 2.375 ± 0.74 to 2.25 ± 0.71 even if insignificant (p Wilcoxon = 0.382 > 0.05), BODE index significantly improves from 4.625 ± 2.13 to 4.00 ± 1.77 (p Wilcoxon = 0.031 < 0.05) and the need for doses of salbutamol as rescue medication significantly decreases from 2.00 ± 1.07 to 1.00 ± 0.93 (p Wilcoxon = 0.021 < 0.05) (Table III).

Table III

Characteristics of the patients from the 2nd group during the study

Characteristics	Baseline	After 60 days of treatment with 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 Moderate Severe	 5 3		
Previous medication Budesonid-Formoterol Fluticasone-Salmeterol	 7 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 dyspnoea 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

Abbreviations: BMI: body-mass index; FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity; SpO_2: peripheral capillary oxygen saturation; mMRC: modified Medical Research Council; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity.

Characteristics of the patients from the 3rd group after 60 days of treatment. The patients of the third group, who maintained the treatment with tiotropium, had constant parameters compared to baseline (Table IV).

Table IV

Characteristics of the patients from the 3rd group during the study

Characteristics	Baseline	After 60 days of treatment with tiotropium	p-value
Patients	8		
Age (years)	71.00 ± 7.52		
Sex (male/female)	5/3		
BMI (kg/m^2)	26.5 ± 5.18		
Severity of airflow limitation Moderate Severe	 5 3		
Previous medication Tiotropium	 8		
FEV1 %	54.375 ± 13.64	54.75 ± 12.84	0.442
FEV1/FVC %	57.75 ± 6.16	57.875 ± 5.74	0.732
SpO_2 %	95.75 ± 2.60	96.375 ± 1.85	0.180
mMRC dyspnoea scale	2.125 ± 0.64	2.125 ± 0.64	0.999
BODE index	4.00 ± 2.56	4.00 ± 2.39	0.999
Rescue medication	1.75 ± 1.28	1.75 ± 1.28	0.999

Abbreviations: BMI: body-mass index; FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity; SpO_2: peripheral capillary oxygen saturation; mMRC: modified Medical Research Council; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity.

Performing ventilatory tests at the beginning and at the end of the study, we noticed a significant improvement of FEV1% values after 60 days of treatment for the patients from the 1st (treated with indacaterol) and 2nd (who received new treatment with tiotropium) groups. As expected, for the patients who maintained treatment with tiotropium (control group) the changes in FEV1 % values were not significant (p Wilcoxon = 0.442 > 0.05), because the regimen of these patients was unmodified.

Our results are in accordance with those reported in other studies [8, 14, 21]. Analysing FEV1 values on 153 COPD patients after 14 days of monotherapy with indacaterol 150 μg and 300 μg, tiotropium 18 μg and *placebo*, Vogelmeier et al. (2010) noticed that increased FEV1 vs. *placebo* was 170 mL for the dose of 150 μg indacaterol, and 150 mL for the dose of 300 μg indacaterol [23]. A study on 311 smokers COPD patients treated with tiotropium 18 μg or *placebo*, with mean values of FEV1 of 1.11 L (tiotropium group) and 1.13 L (*placebo* group) showed, after 12 weeks of treatment, that the average FEV1 values in patients treated *de novo* with tiotropium increased significantly by 102 mL, compared to the placebo group. Moreover, in the current smokers, mean FEV1 increased by 138 mL and in former smokers with 66 mL, which indicates that tiotropium improves lung function regardless of smoking status [15]. In a study on 244 patients with moderate COPD treated with tiotropium or *placebo* conducted over 12 weeks, was obtained an average increase of 166 mL of FEV1 values in tiotropium group compared with *placebo* group, with a similar rate of occurrence of adverse effects [9].

In our study we observed a significant decrease between the initial and final values BODE index score after 60 days of treatment, for the 1st group patients (treated with indacaterol) and 2nd group patients (treated *de novo* with tiotropium), while for the patients of the control group changes were virtually non-existent (p Wilcoxon = 0.999 > 0.05). BODE index can describe functional status in patients with exacerbations of COPD. Bu et al. (2011) monitored 56 patients with moderate to severe COPD by measuring BMI, spirometric tests, mMRC dyspnoea scale and by performing six minutes' walk-test (6 MWT). They noted the duration of exacerbations and their frequency. After two years of follow up, BODE index increased in 33 patients, remained stable in 18 patients, and decreased in five patients. Patients who presented an increased BODE index had significantly more hospitalizations and longer duration of hospitalization than patients with stable BODE index. Among the 33 patients with increased BODE index, 20 patients had lower 6MWT, higher scores mMRC scale indicating a deterioration of functional status, and 13 patients had more advanced air obstruction. Between these two groups, patients with low pulmonary functional status had more frequent exacerbations, with longer duration of exacerbations and longer hospitalizations. Changes in the BODE index can describe altered functional status in patients with COPD [3].

COPD is one of the most common diseases of the elderly. Using GOLD classification, the US prevalence of patients at least GOLD stage II was 1.9 % in subjects between 40-49 years compared with 19.2 % in those over 70 years. There was a doubling in the prevalence of COPD with each decade of age [10]. COPD is in the fifth place of admissions for patients aged over 75 years, patients with more comorbidities that significantly increase the costs [13]. Symptoms of COPD in the elderly

are nonspecific, with a late diagnostic. The vast majority of COPD patients are current or former smokers. Dyspnoea, cough and limitation of physical activity are the most common symptoms, but they are characteristic to other pathologic entities such as heart diseases or other lung diseases. Elderly avoid physical activity just to prevent dyspnoea. COPD exacerbations are common in patients with severe and very severe disease with progressive dyspnoea, cough and purulent sputum, requiring treatment changes.

Miravitlles et al. (1999) observed that the number of exacerbations depends on the severity of the disease. Thus, patients with FEV1 < 40 % of predicted had an average of 2.3 exacerbations per year, whereas patients with FEV1 > 60 % showed only 1.6 exacerbations per year [14]. Treatments with inhaled bronchodilators are at the forefront of COPD management. A meta-analysis conducted by Chung (2013) evaluated the efficacy and safety of indacaterol compared with *placebo*, with other available bronchodilators and as add-on treatment to tiotropium. It was analysed changes in FEV1 values at 12 weeks and secondary parameters such as changes in St George's Respiratory Questionnaire score, BODE index at six months, exacerbations in one year and worsening of symptoms. They analysed 12 controlled trials. Compared with placebo, indacaterol improved FEV1 values by an average of 0.16 L. In addition, indacaterol significantly improved all secondary parameters except the number of exacerbations. Effectiveness of indacaterol was similar to salmeterol, formoterol and tiotropium. The use of indacaterol associated with tiotropium produced significant improvement of FEV1 values. Indacaterol is a good alternative to other bronchodilators or in combination with tiotropium in COPD patients who do not respond adequately to treatment [7]. Hataji et al. (2013) analysed 23 patients with stable COPD instructed to carry an accelerometer for 4 weeks without indacaterol therapy and then for another 4 weeks period receiving indacaterol therapy. All patients were monitored for FEV1 values and performing 6 MWT. After 4 weeks of indacaterol treatment FEV1 values increased significantly, as well as distance travelled in 6MWT. Also, the number of steps, duration of exercise and energy expenditure was significantly improved after treatment with indacaterol. The study concludes that indacaterol improves physical activity in COPD patients [11].

The patients with frequent exacerbations have less chance of long term survival and old age is a risk factor for increased frequency of exacerbations. The consequences of exacerbations significantly differ in elderly compared to middle age COPD patients. Therefore, administration of daily doses of oral vitamin D3 over cold season in temperate zones may reduce the incidence of acute respiratory tract infections [16]. For example, elderly patients have difficulties in the elimination of secretions due to their inefficient cough; also, in the elderly, the metabolism and elimination of the therapeutic agents are affected, thereby increasing the risk of side effects. At patients with COPD the administration of theophylline was associated with substantial reduction in sputum neutrophils, interleukin-8 concentration and neutrophil chemotaxis [20].

Singh (2013) studied 15 patients with moderate and severe COPD treated with indacaterol for minimum one year, with a follow-up of 12-27 months. Indacaterol was associated with significant reductions in the frequency of exacerbations compared with the 12 months prior to follow-up period. In patients who had three or more exacerbations per year, the average rate of exacerbations decreased from 5.43 ± 1.07 to 2.43 ± 0.2 after 12 months of treatment with indacaterol. Reducing dyspnoea was noted in 53 % of patients and exercise tolerance was improved for 67 % of patients. Indacaterol was effective both alone and in combination with tiotropium. Replacing previous treatment with an association β2-agonist-inhaled corticosteroid by indacaterol, as in our study, significantly reduced the number of exacerbations and improved quality of life [22].

Indacaterol once daily resulted in 24-h bronchodilatation in elderly patients with moderate-to-severe COPD. In our study, the bronchodilator efficacy of indacaterol appears to be at least comparable with tiotropium. As the whole world economy was affected lately by the financial crisis, it was clear that the Romanian pharmaceutical market could not have remained untouched [19]. In this context, the use of bronchodilators administered in a single daily dose decreases the number of exacerbations, increases patient compliance, lowers the total costs and reduces the burden on the health system.

Conclusions

GOLD guidelines recommend long-acting bronchodilators as first choice in the treatment of moderate and severe COPD. In our study we can conclude that by using long-acting bronchodilators, administered in a single daily dose, we achieved significant improvement in lung function, amelioration of exercise tolerance and improvement of life quality in elderly COPD patients. The appearance of indacaterol in the pharmaceutical market of Romania provides a long-acting β2-agonist that can be used in monotherapy and improves patient adherence to medication, especially for those patients over 65 years old.

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