Review

Considerations on the Bronchodilator Therapy in Elderly Patients with Obstructive Bronchial Syndrome

S. BERBECARU-IOVAN[1], FLORICA POPESCU[2], ANCA BERBECARU-IOVAN[2]

[1]Medical Semiology, Department III (Medical Specialties I), Faculty of Medicine, University of Medicine and Pharmacy Craiova
[2]Pharmacology, Department II, Faculty of Pharmacy, University of Medicine and Pharmacy Craiova

ABSTRACT: Aging process is related to important anatomical, physiological and psychosocial changes with a significant impact on the management of obstructive respiratory diseases (asthma and chronic obstructive pulmonary disease - COPD). Age-related changes are responsible for different efficiency of bronchodilator drugs on elderly patients compared to younger subjects. Moreover, physiological involution of organs and frequent comorbidities often interfere with the pharmacokinetics of bronchodilators used for asthma and COPD. This study will focus on the use of bronchodilator medication (beta 2-agonists, anticholinergics and methylxanthines) in elderly concerning therapeutic targets to be achieved and adverse effects. Use of bronchodilators, otherwise absolutely necessary for the treatment of obstructive pulmonary diseases, involves significant risk in geriatric patients, requiring careful monitoring of this population.

KEYWORDS: *bronchodilators, asthma, COPD, elderly*

Introduction

Chronic obstructive pulmonary disease (COPD) affects 10% of the general population, and its prevalence reaches 50% in heavy smokers [1]. Because increasing age is strongly associated with an increasing prevalence, COPD requiring medical attention usually occurs late in life, and it is expected to become the third leading cause of death and disability worldwide by the year 2020 [2]. The prevalence of COPD in individuals 65 years of age and older was recently estimated to be 14.2% (11 to 18%) compared with 9.9% (8.2 to 11.8%) in those 40 years or older [3].

Treatment of COPD in elderly patients is an important subject since aging affects the structure, function, and control of the respiratory system. Both lungs and chest wall, including the respiratory muscles, undergo changes that can affect respiratory function [4-6]. The elastic recoil of the lungs is the major determinant of maximal expiratory flow and is diminished with aging, causing increased lung compliance at high lung volumes [4-6]. Bronchiolar diameters diminish and alveolar ducts enlarge as a result of the change in lung matrix and elastic properties of lungs. These changes result in decreased expiratory flow and decreased surface area for gas exchange, respectively.

Pulmonary functional reserve declines in elderly patients [4]. In nonsmoking men, forced vital capacity (FVC) decreases between 0.15 and 0.3 L/decade, and the forced expiratory volume in 1 second (FEV_1) decreases by 0.2 to 0.3 L/decade. These changes are smaller and more gradual in women. Although total lung capacity (proportional to height) does not change significantly with age, residual volume (RV) increases as a consequence of higher closing volume. Control of ventilation is modestly compromised, with blunted responses to hypoxemia, hypercapnia, and mechanical loading. Age-related changes in lung mechanics may be responsible for less effective bronchodilator treatment and also associated comorbidities with hepatic, renal or cardiovascular diseases in these patients may interfere with the pharmacokinetics of bronchodilators used to treat asthma or COPD. In addition, age is characterized by impaired memory, decreased muscle strength and coordination, visual and auditory disorders that reduce handling devices for inhaled treatment causing changes to their treatment schedule, forgetting some doses or administering additional doses. Adverse reactions related to polypharmacy and existing comorbidities are more common in the elderly, and we consider that, on the one hand, bronchodilators may influence cardiac arrhythmia, and on the other hand, concomitant use of medications such as beta blockers or non-steroidal anti-inflammatory drugs (NSAIDs) contributes to worsening bronchoconstriction.

The therapeutic strategy

The goals of COPD management are to reduce long-term function decline, prevent exacerbations, reduce hospitalizations and mortality, relieve disabling dyspnea and improve exercise tolerance. Achieving these objectives is more difficult in the elderly patients and the treatment should be individualized to maintain an acceptable level of health-related quality of life. The treatment of COPD in the elderly is the result of a compromise between therapeutic needs and individual limitations. Besides the pharmacological therapy there are several nonpharmacological interventions that have been shown to improve outcomes and their use in older COPD patients like smoking cessation, influenza vaccination, physical activity, nutritional supplementation, pulmonary rehabilitation and noninvasive ventilation. Bronchodilators, long-acting β_2 agonists and anticholinergics are the mainstay of pharmacologic therapy. Methylxanthines could be an adjunct to first line therapy if symptoms persist or if patients have trouble using inhaler devices [7].

International guidelines for the treatment of asthma and COPD have identified four important factors for an appropriate therapeutic control: creating a partnership between doctor and patient, objective monitoring, environmental control and pharmacological therapy. Important is the partnership between doctor and patient which gives elderly patients ability to adapt single doses depending on the symptoms and/or spirometric monitoring, which requires prior assessment of mental, social and economic status. Ambient control is a difficult task since many elderly patients with respiratory pathology living in polluted indoor climate due to poor hygiene. Also, in terms of objectively monitoring symptoms, elderly patients may have difficulty in assessing the severity of dyspnea compared with younger patients. Is mandatory assessment and monitoring of lung function by repeated spirometry [8, 9].

Inhalation devices

The ideal management for asthma and COPD at any age is the inhalation therapy, since inhalation route allows a rapid achievement of therapeutic effect and significantly reduces side effects due to less systemic distribution [10, 11].

The most common devices used for the inhalation therapy is the administration of bronchodilators as pressurized aerosol devices with controlled release (metered-dose inhalers - MDI) that require some dexterity for an appropriate use and the therapeutic benefits depend on the correct inhalation technique. It has been shown that at least one out of two patients inhaled aerosols users, especially the elderly, have real difficulty of use this devices due to the presence of hands arthritis, muscle weakness, a poor dexterity, visual impairment, poor coordination between actuation and breath or absence of apnea after inhalation [12]. A survey conducted in patients over 65 years showed that only 10% of them can properly handle pressurize aerosol devices. In fact, many elderly patients, who initially have adequately learned the inhalation technique, a few months later, at a subsequent visit, show difficulties due to some cognitive impairment that can be assessed before treatment by a mental state assessment test (Mini Mental State Examination - MMSE). Based on this test, it can be assumed that patients with less than 23 points (maximum of 30 possible) will have difficulty in taking inhaled aerosols [13]. In addition, hypoxia associated with COPD leads to structural brain abnormalities and it can damage the function of neurotransmitter systems involved in both cognition and mood, resulting in neurocognitive deficits and functional impairment [14]. The use of spacer units improves the efficacy of drug delivery by reducing the need to coordinate inspiration with MDI actuation. Based on these considerations, the NICE guidelines (National Institute for Clinical Excellence) for management of COPD in the elderly support the use of pressurized inhalation device only with a spacer device [10].

An alternative solution is the breath actuated inhalers (BAI) that do not require manual activation, it automatically releasing the substance in the presence of inspiration. A study of patients aged 63-85 years showed an increased efficiency of conventional devices to pressurized BAI. BAI is preferred by 64% of patients [15]. Some concerns about the use of BAI in the elderly have been raised. Ho and colleagues examined patients aged over 70 years living in their home (excluding those with impaired cognitive functions and those institutionalized in care homes) for the type of inhaler device used and the ability of patients to use those devices. On a sample of 423 elderly they found that MDI with spacer were used adequately by every patient. Thus, 18.7% of the patients studied had been on inhaled medication with 2.8% of them using two types of devices. Of the 91 devices used, 42.8% were MDI, 37.4% MDI with spacer, while only 19.8% were BAI type devices [16].

Nebulizers are commonly used to administer bronchodilators in the elderly and they are preferred because it can "feel" the treatment. In a study on elderly patients (range 60-91 years, mean age 68 years) hospitalized for exacerbations of COPD has been shown that MDI with spacer or nebulizer have similar results to improve expiratory volume per second (FEV_1), forced vital capacity (FVC) and dyspnea without significant adverse effects on heart rate or on the blood pressure [17].

In a sample of 24 patients with severe COPD (between 57-83 years with a mean of 72 years) found that 5 mg/ml salbutamol administered by nebulization leads to more rapid improvement (after 5 minutes) dyspnea than 400 mg salbutamol administered via MDI plus spacer, but after 45 minutes there were no significant differences for dyspnea score between the two methods of administration [18].

Dry powder inhalation (DPI) devices offer new opportunities for management of inhaled therapy. A comparison between MDI and three different types of DPI (Turbohaler, Diskhaler and Rotahaler) demonstrated that patients using a Diskhaler made significantly fewer errors than users of MDI devices [19]. A similar study focused this time on elderly patients (range 75-101 years) confirms previous study results. After a comparison between MDI plus spacer, BAI and DPI, the authors demonstrate clear superiority of the results obtained with BAI and DPI [20].

A new type of handheld inhaler device is the soft-mist inhaler (SMI), which produces a slow moving, very fine liquid aerosol. Because the mist is produced over 1.5 seconds instead 0.5 second period with most inhalers, it should allow more flexibility with synchronization between device actuation and inhalation, and therefore may provide greater lower-airway deposition [21].

Bronchodilator therapy

Inhaled β_2-agonists

Ageing is associated with increased sympathetic nervous system activity, as demonstrated indirectly by high plasma levels of noradrenaline in the elderly compared to younger individuals and confirmed by records microneurographic post-ganglionic sympathetic nerve activity in skeletal muscle [22].

Therefore, it was suggested an alteration of bronchodilator response to β_2-agonists in the elderly, which is observed in studies on the response to isoprenaline on guinea pig tracheal ring preparations or rats harvested at different stages of maturation [23]. There is a reduction in airway muscle sensitivity to catecholamine during aging, due to lower density of β-adrenoceptors although they are not involved in producing physiological responses. At least in rats, it was shown that the response to hypoxic stress increases β-adrenoceptors lung density, a process which is not affected by age. Also, impaired β-adrenergic activity in the elderly has been studied at postsynaptic level were it was observed a decrease in basal levels of cAMP, second messenger response to β-stimulation in vascular smooth muscle of old animals compared to younger one; decrease of five-time cAMP levels was noticed in studies on tracheal smooth muscle of older bovine [24].

Inhaled short-acting β_2-agonists (salbutamol, terbutaline, levalbuterol) are the most effective bronchodilators in asthmatic patients, regardless of age. Their main therapeutic action is the rapid relaxation (in 10 minutes) of bronchial smooth muscle with duration of action of 4-6 hours and their use is on demand in managing acute bronchoconstriction. In chronic treatment, they were replaced with long-acting β_2-agonists, with over 12 hours duration of action salmeterol (onset of action up to one hour) and formoterol (onset of action within minutes), administered twice daily, without demonstrable tachyphylaxis with regular use.

The role of β_2-agonists in asthma management in the elderly has been little studied. Thomson and colleagues showed that the optimal dose of formoterol in elderly patients is the same as in younger patients, appreciating that formoterol administered via DPI device is superior to both the effectiveness and tolerability as compared to salbutamol in elderly patients with reversible obstructive airway pathology [25]. In a study on healthy subjects about the bronchodilator effect of salbutamol on bronchoconstriction induced by methacholine it was observed that the older group (60-76 years) had a weaker bronchodilator response to salbutamol due to the dependent of age decrease of airway β_2-adrenoceptor responsiveness [26]. Those findings were contradicted by a study that investigated the effects of age on bronchodilator response in severe acute asthma, which concluded that age is not a predictor of response to β_2-agonists, so patients with acute asthma, both young and old, had a similar bronchodilator response to salbutamol measured as percentage improvement in FEV_1 [27]. On the other hand, in the same study, the older group found a significant increase in heart rate with a high incidence of nausea and tremor occur [25]. A study conducted on 16 patients with moderate COPD, aged 51-77 years (mean age 69 years), compared the effect of formoterol, administered as DPI with the effect of salbutamol, administered as MDI. The results showed that both substances induced significant dose-dependent changes in FEV_1 and FVC from baseline levels. However, both formoterol and salbutamol (doses of 48, respectively 800 mg per day) improve FEV_1 less than 200 ml, more significant changes were observed regarding FVC [28].

At usual doses, side effects of inhaled β2-agonists are rare in younger patients and include muscular tremors and nervousness. These substances can have significant side effects in elderly patients, particularly on the cardiovascular apparatus. For these reasons, oral preparations of β_2-agonists are avoided in the elderly, inhalation is the recommended route. β_2-agonists adverse effects are dose dependent and include increased myocardial oxygen consumption, increased blood pressure, arrhythmias, hypokalemia, nausea and tremors. Some of them are at risk of sudden death in certain groups of patients (especially those with ischemic heart disease) at any age. Other adverse effects, such as tremor or changes in blood pressure, considered minor in adult patients, may have a greater importance in elderly patients. Some of the side effects can be amplified due to concomitant use of other drugs, such as hypokalemia, which may be aggravated by diuretics, corticosteroids or theophyllines. Thus, Au and colleagues stated that there is an association between the use of inhaled β_2-agonists and increased risk of unstable angina and myocardial infarction. It has been shown that patients of 68 ± 11 years, β_2-agonist inhalers users at least three months before admission, had increased risk of acute coronary syndrome and that the risk is dose dependent [29].

Anticholinergics

Anticholinergics, including atropine, are used traditionally as asthma, but their administration was accompanied by powerful adverse effects such as urinary retention or increased intraocular pressure, reasons which limit their use in the elderly population with high prevalence of prostate adenoma and glaucoma. Introduction of inhaled preparations characterized by low systemic absorption reduced the risk of adverse effects up to scratch.

If age-dependent changes in adrenergic receptors have been relatively well studied, little is known about any given age-related changes in the cholinergic receptor. However were investigated age-related changes in a study about responsiveness of animal-isolated tracheal tissue to carbacol and acetylcholine [30]. Also it has been studied airway smooth muscle responsiveness to cholinergic in guinea pigs with comparable values in both young and adult animals [31]. It is worth mentioning that were discovered muscarinic M_2-receptor antibodies in healthy individuals of different ages and the incidence of these antibodies increases with age, so it is possible to claim that aging reduce both the number and the functionality of the muscarinic M_2-receptor in the lung. Under normal conditions, presynaptic M_2 muscarinic receptors limit the release of acetylcholine from parasympathetic nerves, so the loss of M_2 muscarinic-receptors leads to increased acetylcholine release and subsequent increased vagal tone [32]. Short-acting anticholinergic preparations (ipratropium, oxitropium) can have effects lasting up to eight hours following administration, while the long-acting preparation (tiotropium) has effects that last more than 24 hours. Anticholinergic drugs have an antagonistic action on the effects of vagal activity in the respiratory system acting especially by relaxing bronchial smooth muscle and by inhibiting bronchial glands in the submucosa.

A comparison on the bronchodilator response to β_2-agonists and anticholinergics, found that patients with chronic bronchitis respond better to taking anticholinergics, whereas asthmatic patients have a better therapeutic response to the use of inhaled β_2-agonists. Although it is recognized a decrease in bronchodilator effect with age for both types of substances, there are results stating that elderly patients (over 60 years) have a better response to administration of anticholinergic agents compared with younger patients who have a better bronchodilator response to β_2-agonists. Other studies have claimed beneficial effect of supplementation regimen of inhaled anticholinergics in elderly patients with poorly controlled asthma even with high doses of inhaled corticosteroids [33].

Tiotropium, last appeared anticholinergic drug is characterized by selectivity for M_1 and M_3 subtype receptors, while having long-term action, requiring a single daily administration compared to his precursors, ipratropium (four times daily) and oxitropium with two administrations per day [34]. A comparative study on the effectiveness and safety profile of tiotropium and ipratropium, demonstrated significantly greater effectiveness of tiotropium compared to ipratropium, with a similar safety profile. Simple regimen with a single daily administration of tiotropium recommended this drug in treatment of geriatric patients [35].

Adverse effects of inhaled anticholinergics include only unpleasant taste and dry mouth. Dry mouth is the only side effect of tiotropium compared with ipratropium groups and placebo [36]. Usually, inhaled anticholinergics have no adverse effects on cardiovascular and respiratory systems. Home treatment with ipratropium was associated with a small increased risk of death in patients with asthma, whereas in patients with COPD ipratropium use has not been linked to increased mortality [37].

Methylxanthines

Despite current COPD guidelines indicating that theophylline is of limited value in the management of COPD, clinical trials support its usefulness in patients with stable COPD, there is a worsening of clinical status when theophylline is withdrawn and treatment with low-dose theophylline significantly reduces neutrophils and myeloperoxidase in the induced sputum of patients with COPD [38]. Theophylline, bronchodilator agent used for a long time in treatment of asthma and COPD, inhibit phosphodiesterase, the enzyme that hydrolyzes cAMP. On isolated guinea pig tracheal tissue, the action of theophylline decreases steadily with increasing age of the animal, suggesting either low efficiency of theophylline as phosphodiesterase inhibitor or the low level of cAMP affects the response to theophylline in aged tissue, therefore it is necessary higher doses of theophylline to produce the same degree of relaxation of airway smooth muscle [30]. Unfortunately, theophylline has a narrow range of action and its bronchodilator effect has a linear relationship with logarithmic increases in serum concentration so the use of theophylline as first-line bronchodilator has been replaced by safer and more potent preparations such as β_2-agonists and anticholinergics [39]. In particular when used in elderly asthmatic patients, dosage adjustments of theophylline is mandatory since their pharmacokinetic profile is different in these patients who are exposed to a number of risk factors that may increase the plasma levels of theophylline. Geriatric patients have a greater risk to develop theophylline toxicity than younger ones, due to the numerous existing comorbidities such as liver dysfunction or heart failure and concomitant use of other drugs who may interfere with the metabolism of theophylline. Thus, carbamazepine, phenobarbital, phenytoin and rifampicin decrease serum levels of theophylline, while other drugs such as allopurinol, cimetidine, clarithromycin, ciprofloxacin, erythromycin, propranolol, ticlopidine or verapamil increase plasma levels of theophylline.

Cardiovascular adverse effects of theophylline are supraventricular tachycardia or potentially fatal ventricular arrhythmias with increased risk in elderly patients. A large study conducted for the Japanese elderly (over 65 years) with asthma or COPD treated with theophylline 400 mg per day for 1-6 months. Were included 3798 patients with a mean age of 73.8 years of which 1997 patients with COPD. Were observed adverse effects related to theophylline in 4.7% of patients, most commonly nausea (1.05%), decreased appetite (0.56%), hyperuricemia (0.42%), palpitations (0.39%) and increased alkaline phosphatase (0.28%). It was reported the presence of seizures. The incidence of adverse effects of theophylline was higher in patients with liver disease and arrhythmias. Plasma levels of theophylline measured in 736 patients was ≤ 15 mg/ml in 87.1% of them [40].

A more recently introduced drug, roflumilast, a phosphodiesterase 4 inhibitor was shown to improve lung function and to reduce exacerbations in COPD populations whose mean age was about 65 years [41].

Conclusions

Advanced age is a significant predictor for poor adherence to pharmacological therapy, contributing to this regimen complexity coupled with memory loss and cognitive impairment.

The obstructive bronchial diseases treatment goals in the elderly include prevention and treatment of symptoms, maintaining an acceptable level of physical activity and improving lung functionality with minimal side effects from the medication used. In the long term, the main objective is to reduce decline in lung function and mortality.

Progress in the treatment of obstructive airway diseases increased life expectancy of these patients, extending the interval between onset and death. These patients survive for a longer period of time despite deteriorating respiratory function, having an important impact on health services due to the significant increase in the number of elderly patients with asthma and COPD.

Use of bronchodilators involves significant risk in geriatric patients, requiring careful selection of inhalation devices, monitoring their proper handling, dosing compliance, concomitant medication control and monitoring of potential adverse effects.

Disclosures

The authors declare no conflicts of interest.

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Corresponding Author: S. Berbecaru-Iovan MD, PhD Student, University of Medicine and Pharmacy of Craiova, str. Petru Rares No 2, 200456, Craiova, Romania; e-mail: sberbecaru@yahoo.com