The use of bronchodilators in the treatment of airway obstruction in elderly patients

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Abstract

Ageing is associated with important anatomical, physiological and psychosocial changes that may have an impact on the management of obstructive airway diseases (asthma and chronic obstructive pulmonary disease (COPD)) and on their optimal therapy. Ageing-related modifications might be responsible for a different effectiveness of bronchodilators in the elderly patients as compared to younger subjects. Furthermore, the physiological involution of organs and the frequent comorbidity, often interfere with pharmacokinetics of bronchodilator drugs used in asthma and COPD. This review will focus on the use of bronchodilators in the elderly, with particular attention to the achievable goals and to rationale, utility and pitfalls in using the inhalation therapy in this age group. \(\beta_2\)-agonists, anticholinergics and methylxanthines will be discussed and their side effects in the elderly will be considered.

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1. Introduction

Management of asthma \cite{1} and chronic obstructive pulmonary disease (COPD) in the elderly is a topic of increasing interest since ageing is associated with important
anatomical, physiological and psychosocial changes that may have an impact on obstructive diseases and on their optimal therapy. Stiffening of the chest wall, reduction of lung elastic recoil and diminished respiratory muscle strength are known to affect respiratory mechanics in this type of population [2]. The loss of the lung elastic recoil due to aging results in reduced maximal expiratory flow rates and in an increase of the resting functional residual capacity.

Ageing-related modifications in lung mechanics, in receptor populations, in nervous control, etc. are likely to interfere with clinical presentations. In comparison with younger subjects, these modifications might be responsible for a different effectiveness of bronchodilators in the elderly patients. In addition, changes in organs or systems other than lung (liver, kidney, heart), either due to physiological involution or to frequent comorbidity, often interfere with the pharmacokinetics of the bronchodilator drugs used in asthma and COPD.

Furthermore, older age is characterized by various aspects of disability (memory problems, loss of coordination and muscle strength, hearing and visual loss) that may often decrease the ability to regularly follow the treatment schedules or to handle complex devices, such as metered-dose inhalers (MDI) or powder dispensers, thus limiting the compliance to the prescribed therapy.

Adverse reactions related to polypharmacy and comorbidity are more frequent in the elderly: on one hand, bronchodilators might worsen coexisting diseases (such as cardiac arrhythmias); on the other, medications often used by elderly patients, like β-adrenergic blockers or non-steroidal anti-inflammatory drugs, might elicit or worsen bronchoconstriction.

Therefore, particular attention should be paid to the adaptation of treatment schedules for asthma and COPD in the elderly and above all to the specific issue of bronchodilators. The present review will be focused on this issue.

2. Adaptation of treatment strategy

Asthma control in the elderly cannot be achieved without an appropriate treatment strategy that takes into account the age-related peculiarities of this patients group. The international guidelines for treatment of asthma in the elderly [1] identify four “components”, which are of prominent importance in the management. Although these components are similar to those for adults, they have been adapted to the peculiar characteristics of the older age. The four identified components include: creation of a partnership between patients and physician, objective monitoring, environmental control and pharmacological therapy. Among them, the creation of a partnership is particularly critical in the aged: the involvement of the elderly in an active partnership, e.g. leading the old patient to share the responsibilities of self adaptations of medications is a difficult task, which requires a preliminary and careful evaluation of mental status, of mood, of social and economic constraints. Not easier may be the task of environmental control since in the majority of cases the elderly respiratory patient’s life is restricted in confined environments, exposed to a substantially greater risk of indoor pollution due to poor hygiene. Similarly, the objective monitoring and pharmacological therapy deserve a special attention from physician when the attended patient is an old man or woman.

The specific need of a careful objective monitoring comes out from the observation that the elderly asthmatics have a blunted sensitivity to dyspnea-related stimuli compared with younger patients [3,4]. The clinical implication of this finding is that elderly patients might be less aware either of the presence or severity of the bronchoconstriction. Therefore, spirometric assessment and monitoring of the lung function with appropriate methods is mandatory. In spite of physical and mental limitations, that frequently affect these subjects, a reliable spirometry may be obtained in the vast majority of the elderly ambulatory patients, as demonstrated by a multicenter study based on a rigorous quality control program [5].

3. Goals in the use of bronchodilators in the elderly

Asthma and COPD are chronic diseases in which therapeutic intervention aims at controlling symptoms and, if possible, at slowing down the loss of lung function over the time that characterizes these diseases to a various extent. The achievement of the desired therapeutic and clinical goals may be more difficult in the elderly rather than in the younger patients. Therefore, treatment should be individualized to each specific condition.

One of the most important goals of treatment is maintaining an acceptable level of health-related quality of life. However, treatment itself may be a burden, particularly in case of a cumbersome and costly schedule. This may contribute to the impairment of perceived health status of elderly patients, particularly in case of administration of multiple drugs and use of complex inhalation devices. As consequence in the elderly much more than in any other age group, the choice of optimal treatment of asthma and COPD should be the result of a reasonable compromise between medical needs and individual limitations. In this perspective, application of tailored educational and training programs for the use of suitable medications and devices could contribute to achieve the best possible results in individual patients.

4. Inhalation therapy

Inhalation therapy is the method of choice for asthma and COPD management. It is the most important and effective way to administer bronchodilators in all ages [6,7]. In addition, inhalation route allows a more rapid achievement of therapeutic effect and reduction of side effects because of lesser systemic distribution of the drug [8].
MDI are the most common devices used for inhalation therapy. They are characterized by different shapes and complexity and some of them require more manipulation and dexterity than others. Therefore, often the elderly patients do not use them as friendly as desirable. This limitation might potentially be of great impact on the effects of the treatment since therapeutic benefit depends mainly on the rate of deposition of drugs in the airways and this, in turn, is largely determined by a correct inhalation technique [9,10].

It has been shown that one out of two patients is not able to use MDI in a satisfactory way [11]. This problem is more evident in the elderly patients than in the younger ones [12]. Reasons include hand arthritis, muscle weakness, poor dexterity, visual impairment, which may result in failure to shake the device, poor coordination of actuation with inhalation and absence of breath holding. A community survey, carried out in patients aged 65 years and over, has shown that only 10% of them managed MDI with an optimal performance. Since it is essential to learn an adequate technique [13] and to retain it [14], it is not surprising that the most important determinant of inhaler technique is cognitive function [15]. Actually, many elderly patients who seem to have successfully acquired an adequate technique with a particular device may demonstrate inadequate technique if assessed a month later [14]. It has been demonstrated that the inability to learn a correct inhalation technique in old age is due to cognitive impairment that can be easily assessed by mini mental test (MMT) [16]. On this basis, the authors point out that a score lower than 23/30 at the MMT could simply identify patients who are at risk of a poor inhalation technique. Furthermore, it has also been documented that those with Hodkinson [17] mental test scores of less than seven over 10 are unlikely to have adequate inhaler technique [16].

The use of spacers or reservoir units improves the efficacy of drug delivery via MDI and their utilization is strongly encouraged. Valved holding chambers of large volume might be more effective than tube spacers [18]. These chambers reduce the need to coordinate inhalation and MDI actuation, allowing the inhalation of the drug held inside the chamber with more than one inspiratory maneuver. As a result, patients with age-related problem in handling MDI can achieve a more effective drug inhalation [14]. Based on this considerations, the NICE guideline on management of COPD reports that the standard MDI, when used in isolation (i.e. without a large-volume spacer device) are rarely appropriate for elderly patients [6].

As mentioned above, the major problem with MDI use is coordination between actuation of the device and inhalation maneuver: an alternative solution to this problem is represented by breath-actuated inhalers (BAI). These devices do not require manual activation but they are automatically triggered by inspiration. A study on elderly patients aged 63–85 years, based on an objective infrared system to detect canister actuation and a spirometer to measure the inspiratory volume, has demonstrated that BAI are successfully used more often than MDI (64% of patients vs. 36%) [19]. Other observations support that breath-actuated devices, such as the Autohaler, are generally used in an easier way by the elderly persons [20,21]. However, some concerns about the use of BAI by the elderly have been raised. Ho et al. [22] studied patients aged 70 years and over living at home (excluding those with cognitive impairment and those in care homes), to investigate the prevalence of inhaler use, the main used inhaler devices and the ability of older people to use the inhalers. On a sample of 423 elderly, they found that not only MDI with large-volume spacers were used adequately by virtually every subject, but also they were more likely to be used correctly than BAI [22]. In addition, this study demonstrated that 18.7% patient used inhalers, with 2.8% using two inhaler devices. Of the 91 inhalers used devices, 42.8% were MDI, 37.4% were MDI with large-volume spacers and 19.8% were BAI. Interestingly, 12% of subjects who rated their inhaler device as being easy to use, made major errors and this was particularly problematic for BAI [22].

Nebulizers are frequently used to delivery bronchodilators in elderly patient, who often seem to prefer this modality. Perhaps this is due to “the feeling of the therapy”, that is the sensation that is given by the taste and by the vision of the drug. In addition, it is possible that the elderly patients are more able to inhale the medications from these devices than from MDI or powder inhaler devices. In a study on elderly patients admitted for acute exacerbation of COPD (mean age: 68; range 60–91 years), it has been demonstrated that MDI delivered through a spacer and nebulizer equally improved FEV1, FVC and dyspnea, without effects on heart rate and diastolic blood pressure [23]. However, severely fatigued or obstructed patients, who lack the ability to use MDI plus spacer, might be better treated by nebulizers.

In a sample of 24 severe COPD patients (mean age 72; range 57–83 years), 5 mg of nebulized salbutamol provided more rapid initial (after 5 min) relief of breathlessness in subjects with COPD than 400 mg salbutamol from an MDI plus spacer [24]. However, there was no difference in breathlessness scores at 45 min between the two modes of delivery [24]. Since the use of local anesthetic applied on the patient’s face did not influence the results, the authors concluded that the difference in the initial response to the treatment might be related to the process of nebulization [24].

Dry powder inhalers offer an additional opportunity in managing inhaled therapy. A comparison between MDI and three different dry powder inhaler devices (Turbohaler, Diskhaler, and Rotahaler) demonstrated that the patients using a Diskhaler made fewer errors, while most of the patients using MDI made crucial mistakes [25]. A subsequent study [26], targeted on elderly people (aged 75–101), confirms these results. After a comparison of MDI with large-volume spacers, breath-activated devices and dry powder inhalers, to the authors demonstrated that
breath-activated and dry powder inhalers were more correctly used than MDI with large-volume spacers [26].

5. Bronchodilators drugs

5.1. Inhaled \( \beta_2 \)-agonists

Human aging is associated with an increase in the activity of the sympathetic nervous system. This is supported by the observations that plasma noradrenaline levels (that are often taken as an indirect index for sympathetic activity [27]) are higher in older subjects compared to younger persons [28] and subsequently it has been directly confirmed by microneurographic recordings of post-ganglionic sympathetic nerve activity to skeletal muscle [29]. This age-related increase in sympathetic activity is mild and develops slowly (10–15% per decade) [29].

As a consequence, an alteration of bronchodilator response to \( \beta \)-agonists in elderly people has been suggested [30]. Age-related impairment in \( \beta \)-adrenoceptor responsiveness has been observed in vivo and in vitro in several organs and systems. Significant age-related changes in isoprenaline potency have been detected in tracheal ring preparations taken from animals during the early maturation phase of animal growth in guinea-pig and rat [31]. Moreover, in rat-isolated tracheal tissue, age-related decreases in fenoterol potency have been observed during senescence, but not during maturation.

Even if an early study suggested a reduction of \( \beta \)-adrenoceptor numbers (density) with age [32], subsequent observations demonstrated that there is no difference in receptor density between young and elderly subjects [33–35]. However, it has been suggested that the relationship with age may be more complex with a peak in density in middle life [36]. Furthermore, treatment with corticosteroids can induce an age-related increase in the potency of a \( \beta \)-agonist due to the increase in the density of \( \beta \)-adrenoceptors [37].

Duncan et al. [38] documented that there is a reduced sensitivity of the airway muscle to catecholamines during aging which may be partly due to the increased density of \( \beta \)-adrenoceptors though they are not involved in eliciting the physiological response. However, at least in rats, the ability to respond to chronic hypoxic stress with increased lung \( \beta \)-adrenoceptor density is unaffected by aging [39].

On the contrary, there is considerable evidence relating the reduction in \( \beta \)-adrenoceptor affinity (or a reduced percentage of high-affinity receptors) with increasing age. Such changes have been demonstrated in human mono-nuclear leucocytes [40] and, in studies carried out on animal lungs, possibly in association with receptor internalization in membrane-bound vesicles [41].

Abnormal post-receptor events may also be implicated in impaired \( \beta \)-adrenergic activity in the elderly. Basal levels of cyclic AMP (cAMP), which is the second messenger involved in the responses elicited by \( \beta \)-adrenoceptor stimulation, have been found to decrease in vascular smooth muscle in old animals compared with younger animals [42,43]. In bovine tracheal smooth muscle, basal cAMP levels were five-fold increased in young compared with old animals [43], and this is consistent with the more elevated adenyl cyclase activity seen in lung from young rat compared with older animals [44–46]. Similarly, the maximum adenyl cyclase response to \( \beta \)-adrenoceptor stimulation has been shown to decrease in the rat liver as the animal reaches maturity [47]. Furthermore, catalytic activity of adenyl cyclase in human mononuclear cells is impaired in old age [33] and similar age-related abnormalities are seen in animal studies on myocardium [45].

Inhaled short-acting \( \beta_2 \)-agonists (salbutamol, fenoterol and terbutaline) are the most effective bronchodilators for patients with asthma, regardless of age. Their main therapeutic action is represented by a rapid (within 10 min) bronchial smooth muscle relaxation that persists over 4–6 h. Their use is fundamental in managing acute bronchoconstriction on demand; conversely for chronic or regular therapy they have been replaced by long-acting \( \beta_2 \)-agonists (salmeterol and formoterol) [48]. The duration of action of the latter class of bronchodilators exceeds 12 h and this allows a b.i.d. administration schedule. It has been demonstrated that for the management of mild-to-moderate asthma, salmeterol administered b.i.d. is superior to albuterol given either q.i.d. or as needed without evidence of tolerance to the bronchodilating effects of salmeterol [49].

Experiences on the role of \( \beta_2 \)-agonists in the management of asthma in the elderly are scanty. A study carried out on bambuterol, which is transformed into terbutaline as active metabolite, has shown efficacy and good tolerability in elderly patients with asthma [50]. Thomson et al. [51] showed that the optimal dose of formoterol in the elderly is the same as for other adults. Moreover, they documented that formoterol given by dry powder inhalation is superior in terms of both efficacy and tolerability to salbutamol in the treatment of elderly patients with reversible obstructive airway diseases [51]. However, Some data suggest that bronchodilator response to \( \beta_2 \)-agonists could be impaired in the elderly. In a study on bronchodilator response to salbutamol and ipratropium, the FEV\(_1\) response to the \( \beta_2 \)-agonist declined with age; conversely, the response to ipratropium was not related to age [52]. The bronchodilator effects of salbutamol after methacholine-induced bronchoconstriction has been tested in a study carried out in healthy subjects [30]. This study has shown that the elderly group (age range: 60–76 years) had a lower sensitivity to bronchodilator effects of salbutamol, and this is interpreted by the authors as due to an age-related decrease in airway \( \beta_2 \)-adrenoceptor responsiveness. Since the study was conducted in healthy subjects, it is not easy to transfer the whole observation to asthma where airway responsiveness could be influenced by disease-related conditions like chronic inflammation and remodelling [53]. A recent retrospective analysis, carried out in subjects with an FEV\(_1\) reduced by at least 20%, has documented that aging does not affect bronchodilator response to
dependent change in FEV1, inspiratory capacity (IC) and result showed that both drugs induced significant dose-treatment. Conversely, a significant increase in heart rate over baseline was seen in the older group, which also presented a higher incidence in nausea and tremor [55]. However, in this study the age groups have been differentiated using the age of 35 years as cut-off level, which obviously is inadequate to allow inferences on the elderly (mean age: 68 years) response to the treatment.

In general, in asthma long-acting inhaled β2-agonists may be helpful as an adjunct to anti-inflammatory therapy (inhaled steroids) in controlling chronic symptoms. Patient using long-acting inhaled β2-agonists should be advised that these drugs are not designed for the treatment of acute symptoms.

In 16 patients (median age 69; range 51–77 years) with mild acute exacerbation of COPD, formoterol as dry powder has been compared with salbutamol [56]. The result showed that both drugs induced significant dose-dependent change in FEV1, inspiratory capacity (IC) and FVC from baseline values. However, either for formoterol or for salbutamol at the maximum dosage (cumulative doses: 48 and 800 μg, respectively), the FEV1 improvement was less than 200 mL whereas greater changes have been observed for IC and FVC [56].

5.1.1. Inhaled β2-agonists side effects

At usual therapeutic doses, side effects of inhaled β2-agonists are rare in young patients and include muscular tremors and nervousness. Conversely, these drugs may have significant side effects especially concerning cardiovascular apparatus in the elderly. For this reason, oral β2-agonists are normally avoided in the elderly and inhalation is the route of choice. β2-agonists side effects are dose-dependent and include: increase in myocardial oxygen consumption and in blood pressure, arrhythmias, hypokalemia [57], nausea and tremor. Some of them (including chronotropic and electrolyte effects) might be life-threatening in susceptible patients (such as patients with ischemic heart disease) at any age; others, such as tremor and blood pressure changes, considered relatively minor in adult subjects, might be important in geriatric patients. Some of these side effects may be increased by concomitant use of other drugs: hypokalaemia could be aggravated by concomitant treatments promoting potassium loss, including diuretics, corticosteroids and theophyllines. In a case-control study, Au et al. [58] reported an association between inhaled β2-agonists and the risk of unstable angina and myocardial infarction. They found that patients (mean age: 68 ± 11 years) who had used β2-agonists in the 3 months preceding the hospital admission had an increased risk of acute coronary syndrome. This risk was dose-dependent and the OR ranged from 1.55 for one-to-two MDI canisters to 3.83 for six or more canisters, after adjusting for age, cardiovascular risk factors (including hypertension and diabetes) smoking history and β-blocker prescription [58].

5.2. Anticholinergics

Anticholinergic antimuscarinic compounds, including atropine, had been used in the treatment of asthma for long; though their use was accompanied by the frequent occurrence of side effects, including decreased urinary flow rate and increased intraocular pressure, that represented an important limitation to their use particularly in the elderly population where the prevalence of prostatic diseases and glaucoma is high. However in recent decades, the introduction of inhaled derivatives characterized by poor systemic absorption has reduced this risk virtually to nil, provided that one takes care that the drug is not nebulized into the eye where it could precipitate glaucoma.

Although age-dependent changes in human adrenergic receptors have been extensively studied, relatively little is known about possible age-dependent alterations in human cholinergic receptors. Significant age-related changes have been demonstrated in the responsiveness of animal-isolated tracheal tissue to carbachol and acetylcholine, modifications which are also species-specific [59]. These changes are not due to modifications in muscarinic receptor number, but to alterations in receptor coupling to post-receptor processes. Conversely, it has been documented that the airway smooth muscle responsiveness to cholinergics is comparable in both immature and adult guinea pigs in vivo [60]. It is noteworthy that antibodies against the muscarinic M2-receptor may be found in healthy subjects of different ages [61]. Interestingly, the frequency of occurrence of these antibodies increased with increasing age in these volunteers. Therefore, it is possible to postulate that during the aging process in humans, number and functional responsiveness of lung muscarinic M2-receptors decrease. Under normal conditions, M2 muscarinic receptors limit the release of acetylcholine from parasympathetic nerves. Hence, loss of M2 muscarinic receptors results in increased acetylcholine release and in increased vagal tone.

Anticholinergic drugs (ipratropium bromide, oxitropium and the more recent tiotropium) have an antagonistic action on the effects of vagal activity on respiratory system. They act especially on bronchial smooth muscle (relaxation) and on bronchial submucosal glands (inhibition of secretion). Comparative bronchodilator responses to anticholinergics and β2-agonists were studied in a controlled clinical trial [62], that tested patients with chronic bronchitis (age: 51 ± 13 years) or asthma (age: 53 ± 13) with mild to moderate airflow obstruction. The results showed that patients with chronic bronchitis responded better to ipratropium bromide, whereas asthmatic patients responded better to salbutamol. Although a linear decline of effectiveness with age was demonstrated for both drugs,
the study showed that older patients (above 60 years of age) respond better to the anticholinergic agent than younger subjects who, conversely, benefit more from salbutamol.

The previous results are in contrast with those from a subsequent study, which compared the potential effect of age on bronchodilator response in stable asthmatic subjects of two age groups (18–25 vs. >65 years) [63]. The authors did not find any difference between salbutamol and ipratropium or between the age groups, and they concluded that age does not modify the response to any drug. Other observations suggest that the addition of regular inhalation of oxicromium is beneficial in elderly asthmatics, whose asthma is not well controlled, even though treated with high-dose inhaled steroids [64].

The effects of inhaled anticholinergic drug in elderly with COPD have been tested to investigate the consequence on exercise capacity and dyspnea. Teramoto and Fukuchi [65] demonstrated that oxicromium improves breathlessness and exercise capacity in COPD patients without differences between elderly subjects (75 years and over) and middle-aged patients (mean age 60.1 ± 1 years). However, the use of an anticholinergic agent may not be sufficient to achieve maximal bronchodilation. In a sample of patients with stable COPD (mean age 67.5: range: 56–78 years), it has been demonstrated that a combination therapy with inhaled salbutamol and ipratropium results more effective than ipratropium alone [66].

More recently tiotropium, a new anticholinergic drug, has been marketed. It is characterized by muscarinic M₁ and M₃ receptor subtype selectivity. Furthermore, it shows a remarkably prolonged activity, which requires one daily administration instead of the usual q.i.d. dispersion of ipratropium and b.i.d. of oxicromium [67]. A multicenter double blind randomized study, that compared efficacy and safety of tiotropium and ipratropium, showed that tiotropium was significantly more effective than ipratropium with a similar safety profile [68]. These data favor the use of tiotropium as the cholinergic antagonistic treatment of choice for the long-term therapy in COPD. The once-daily inhalation schedule of this drug may be particularly favorable in the setting of treatment of geriatric patients, whose cognitive, mood and dexterity limitations exaggerate the problem of compliance. Further specific studies are required to better define the position of this promising drug.

5.2. Inhaled anticholinergics side effects

Properly inhaled anticholinergic drugs are generally safe in the elderly. Commonly reported adverse effects include an unpleasant taste and dryness of the mouth: the latter is the only side effect of tiotropium that occurs significantly more often than in placebo or ipratropium groups [69,70]. Usually, cholinergic inhibitors have shown no cardiovascular or respiratory adverse effects. Although occasional prostatic symptoms have been reported, there are no data to prove a real causal relationship [71].

Treatment with ipratropium bromide at discharge has been reported to be associated with an increased risk of death from asthma [72]. Subsequent observations documented that in patients with COPD the use of this drug was not associated with an increase in mortality, while in asthma this increase was small [73]. It is possible to postulate that the asthmatic patients who received ipratropium suffered from more severe disease. Therefore, the anticholinergic agent should play the role of marker of severity rather than that of causative factor.

### 5.3. Methylxanthines

Theophylline is a bronchodilator agent that has been used for various decades in the treatment of asthma and COPD. Its main mechanism of action is thought to involve inhibition of phosphodiesterase, the enzyme which hydrolyzes cAMP. In isolated tracheal tissue from guinea-pig the potency of theophylline steadily declined with increasing animal age, although no changes in maximum relaxant responses were observed over the same age range [59]. These results suggest that in older animals, theophylline is either less effective as an inhibitor of phosphodiesterase or that lower cAMP levels affect the response to theophylline in aged tissue. Alternatively, this might reflect increased levels of phosphodiesterase with ageing. Hence larger doses of theophylline would be required to produce the same degree of relaxation of airway smooth muscle.

Unfortunately, theophylline has a narrow therapeutic range and its bronchodilator effect has a linear relationship with logarithmic increases in serum concentration. During the last two decades, the clinical use of theophylline as a first-line bronchodilator declined and this drug has been replaced by safer and more potent agents, including inhaled β₂-agonists and anticholinergics. Particularly when used in elderly asthmatic patients, dosage adjustment of theophylline is mandatory since this drug has different pharmacokinetics in the elderly [74], who are exposed to various risk factors that may increase the plasma theophylline level, such as reduced clearance [75–77], various underlying diseases and multiple coadministered drugs. After theophylline treatment has been initiated, elderly patients should be monitored. It has been proposed that, in these subjects, serum concentrations of the drug should range between 8 and 12 μg/ml [1], that is a level lower than the range proposed in the international asthma guidelines for the general population [78]. However, Armijo et al. [79], who studied the steady-state pharmacokinetics of an ultralong-sustained-release formulation of theophylline in elderly hospitalized patients with COPD, documented that there was no significant correlation between the patient’s age and apparent clearance [79]. Inter-patient variability and peak/trough fluctuations with this formulation were higher than those described in healthy volunteers [79].

Nonetheless, elderly subjects are at greater risk of theophylline toxicity than younger individuals especially for a more frequent occurrence of concurrent diseases, such as liver dysfunction, cardiac failure and fever, and for a more frequent use of drugs, which may interfere with
theophylline metabolism. For example, carbamazepine, isoproterenol, phenobarbital, phenytoin and rifampin decrease serum theophylline levels, whereas other drugs increase them: among them are high-dose allopurinol, cimetidine, clarithromycin, ciprofloxacin, erythromycin, estrogens, mexiletine, pentoxyfilline, propranolol, tacrine, ticlopidine, troleandomycin, and verapamil.

5.3.1. Methylxanthines side effects

These drugs may cause cardiovascular side effects such as supraventricular tachycardias and arrhythmias including also potential fatal events like ventricular arrhythmias. In this regard, Shannon and Lovejoy [80] have shown that the influence of age may be even more important than that of peak serum concentration on life-threatening events after chronic theophylline intoxication. In this study, elderly patients had a greater risk of life-threatening events than younger subjects. Furthermore, peak serum theophylline concentration was not a useful predictor of life-threatening events [80].

It is important to underline the possibility that, especially in the elderly, some adverse event, like multifocal atrial tachycardias and arrhythmias, can occur, even if the serum theophylline concentration is within the recommended range [81,82].

A large-scale prospective study [83] has recently been carried out in Japanese elderly (≥65 years old) patients with asthma or COPD who had been treated with sustained-release theophylline tablets at a dose of 400 mg/day for 1–6 months. Among 3798 protocol-complying patients (mean age: 73.8 ± 0.10 years, 1997 with COPD), theophylline-related adverse events were observed in 4.7% of patients. The five most frequently observed adverse events were nausea (1.05%), loss of appetite (0.56%), hyperuricemia (0.42%), palpitation (0.39%), and increased alkaline phosphatase (0.28%). No convulsions were reported; six patients had serious adverse events. The incidence of theophylline-related adverse events was higher in patients with hepatic disease (odds ratio: 1.81) and in patients with arrhythmia (odds ratio: 1.88). Blood drug concentration measurements in 736 patients indicated that the drug levels were ≤15 μg/ml in 87.1% of patients, no correlation was noted between dose and theophylline-related adverse events [83].

On this basis, the recent NICE guidelines on COPD recommend (with a Grade D of evidence) particular caution when using theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities and the use of other medications [6].

6. Conclusion

Progressive improvement in treatment has increased the life expectancy of patients with obstructive airway diseases, extending the interval between the onset of disability and death. Consequently, these patients can survive for a long time in spite of severe respiratory impairment and disability. This has an important impact since the number of elderly patients suffering from asthma or COPD is dramatically increasing.

Unfortunately, the implementation of a safe and effective treatment may be more difficult in such patients. Senescence, extra-pulmonary diseases, malnutrition, polipharmacy may influence presentation and clinical course of asthma or COPD and interfere with their management. In particular, the use of bronchodilators, which may be life saving in obstructive airway diseases, implies a significant risk in elderly patients. For this reason, a careful monitoring of treatment is recommended when dealing with this population.

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