Original Article

ISSN: 1735-0344 *Tanaffos 2012; 11(2): 16-21*

TANAFFOS

Effect of Age on Response to Treatment in Adult Patients with Severe Persistent Asthma

Ebrahim Razi , Gholam Abbass Moosavi, Armin Razi

Departments of Internal Medicine, Kashan University of Medical Sciences, Kashan, Iran.

Received: 23 July 2011
Accepted: 26 December 2011

Correspondence to: Razi E
Address: Department of Internal Medicine, Kashan University of Medical Sciences, Kashan-Iran.
Email address: ebrahimrazi@yahoo.com

Background: Due to current controversies regarding the effect of age on response to treatment in asthmatic patient, the present study was performed on patients referred with acute asthma attack for further evaluation of this matter.
Materials and Methods: In this study 138 patients with severe persistent asthma were enrolled and divided into two categories of young (age ≤35 yrs; 82 cases, mean age = 25.2±7.3 years) and elderly subjects (≥50 yrs; 56 cases, mean age 57.4±6.4 years). Response to treatment was determined by pulmonary function tests.
Results: The mean percentage change of FEV1 from baseline in male and female patients of young and old age was 75.05±46.61 and 71.39±41.30%, (P=0.721) and 100.79±51.34% and 69±37.39% (P=0.015), respectively. The mean percentage of possible improvement of FEV1 among male and female patients of young and old age was 62.81±25.67% and 54.46±23.82% (P=0.148), and 78±24.04% and 63.58±41.24% (P=0.087); respectively.
Conclusion: Response to treatment was significant in both young and old age groups suffering from acute asthmatic attack except for young female patients in which, percentage change of FEV1 increased compared to older patients. Among other patients this value and percentage of possible improvement of FEV1 between the 2 groups did not change significantly and age did not play a significant role in assessing the response to treatment in acute asthmatic attack.

Key words: Severe persistent asthma, Age dependent, Bronchodilator response

INTRODUCTION

Asthma is a condition characterized by variability in airflow obstruction, fluctuation of symptoms, and changes in the level of bronchial responsiveness and airway inflammation. Process of aging influences on the structure and function of the respiratory system and results in loss of elastic support of airways, hyperinflation and relative loss of respiratory muscle strength (1).

Various studies have demonstrated that adrenergic system activity is blunted with aging (2-4). For instance, response to isoproterenol, propranolol, and salbutamol declined significantly in the elderly (2-5).It has been suggested that the mechanism of altered beta-adrenergic sensitivity in the elderly is related to reduction of beta-receptor affinity for agonists (6). It has been suggested that aging is associated with reduction in beta-adrenergic responsiveness (7).

Limited studies are available that evaluate the effects of age on bronchodilator response in asthmatic patients (8,9). Rodrigo et al. in a study that was conducted on patients with acute asthma concluded that age is not a predictor of response to beta-agonists (9). Parker reported that aging does not affect bronchodilator response to beta-agonists following methacholine-induced broncho-constriction (10).

Kradjan et al. reported that both albuterol and ipratropium are effective bronchodilators in young and old asthmatic subjects, and age is not a predictor of response to either drug (8). In another study, Bellia et al. reported that in asthma, aging is associated with a reduced acute responsiveness to bronchodilators (11). They also concluded that patients with early-onset asthma (starting before the age of 40 years), compared to late-onset asthma (starting after 40 years of age) usually have a less reversible airway obstruction and poorer response to pharmacotherapy (11). In asthma, the response pattern is also related to allergy and age. Allergic patients and patients under 60 were more likely to respond better to salbutamol than non-allergic and older patients (12).

The purpose of this study was to evaluate the effects of age on treatment response in two groups of patients with acute asthma and different age range, which were referred to our clinic.

MATERIALS AND METHODS

This study was carried out on 138 patients in a private clinic who were treated for severe persistent asthma, between March 2007 and February 2009, with a 2 week period follow-up.

Patients were considered eligible if they suffered from asthma according to the American Thoracic Society criteria (ATS criteria) (13). The ATS has developed criteria which suggest a significant post-bronchodilator FEV_1 and/or FVC response of 200 mL or greater and 12% improvement from baseline (13). Age-wise, patients were divided into two groups of young (age≤ 35 years), and elderly (≥ 50 years). The participants' age ranged from 15 to 65 years in both males and females; and the diagnosis of severe persistent asthma was made according to clinical findings and FEV1 value ≤ 60% of the predicted (14). Patients classified as severe persistent asthma in this study correspond to the National Asthma Education and Prevention Program classification of severe persistent asthma (14).

Patients were excluded if they were smokers, pregnant, or had developed pneumothorax, emphysema, other acute or chronic respiratory diseases, hypertension, unstable angina, or other prominent cardiovascular diseases. A spirometer (Fukuda St 95, Japan) was used to measure pulmonary function. Spirometry was performed in accordance with the ATS standards for acceptability and reproducibility of the forced vital capacity (FVC) maneuver (13). According to ATS guidelines, accurate spirometry requires three acceptable spirometry tests that demonstrate reproducibility. The FVC and FEV1 values from these three tests should vary by no more than 5% or 100 mL, whichever is greater. Spirometry was performed on patients who received no drugs at least 24 hours before attendance. In all patients, the treatment was adjusted according to the level of severity (15). All patients were treated with an inhalation of Short-acting beta2-agonists for symptom control, along with high dose Fluticasone / salmeterol (250 µg-50 µg) 2 inhalations twice daily, and a short course of oral prednisone (40 -60 mg daily). After two weeks, a new spirometric assessment was performed under the same conditions in all patients. The results of pulmonary function tests for each subject were calculated as percentage of change in FEV1 relative to baseline and as percentage of possible improvement in FEV1 by the following formula:

$$Percentage\ of\ change = \frac{Observed - baseline}{baseline} \times 100$$

$$Percentage\ of\ possible\ improvement = \frac{Observed - baseline}{\Pr edicred - baseline} \times 100$$

where observed is the post bronchodilator value, and baseline is the baseline value on the day of testing. The latter calculation, as advocated by Weber et al (16). allows for a more accurate comparison of response between two populations with different baseline pulmonary function. Response expressed as percentage of change from baseline may be misleading in subjects with lower baseline function compared to those with higher baseline values.

In an earlier study (17), the percentage change of FEV1 after two weeks of treatment was 63±13%. Estimation from power and sample size calculations show that the minimum number of samples in each group was 56 subjects that was sufficient to detect an 8% difference with $\alpha = 5\%$ and $\beta = 0.1$ (*i.e.*, with 90% power).

Data are presented as mean ± SD in parentheses. Baseline data of the two groups were compared by *t* test for independent samples. A p-value <0.05 was considered significant for all statistical tests.

RESULTS

Out of 138 patients that completed the study, 82 were young with a mean age of 25.2±7.3 yrs; (41 males, 41 females), and 56 were elderly with a mean age of 57.4±6.4 yrs; (35 males, 21 females). The baseline characteristics of studied patients are presented in Table 1. There were no significant differences regarding baseline FEV1 level (% predicted) before treatment between the two groups of young and elderly patients.

Table 2 summarizes the value of pulmonary function tests after treatment in both groups. After treatment, mean FEV1 improved significantly in both groups in comparison with its baseline values (p<0.001).

As shown in Table 2, there were no significant differences between two groups regarding the mean± SD FEV1 changes. On the other hand, although there was a difference between two groups concerning the mean±SD of percentage of possible improvement of FEV1, this difference was not statistically significant. The mean±SD of baseline FEV1 value was greater in the young than in the elderly patients (1.57±0.47 lit vs. 1.28±0.38 lit; respectively, p<0.001).

As shown in Table 2, although the mean± SD percentage changes of FEV1 in young patients was more than in the elderly, only in female subjects it was statistically significant (p = 0.015). The percentage change of FEV1 in male subjects was not statistically significant (p= 0.721).

Table 1. Baseline characteristics of pulmonary function tests of both understudy groups (mean ±SD)

Variable	Young patients (n=82)	Elderly patients (n=56)	P value
Male/Female	41/41	35/21	
Baseline FEV1, Lit	1.57±0.47	1.28±0.38	<0. 001
Baseline FEV1,% pred.	45.8±11.8	42±11.4	0.83
Predicted FEV1, Lit	3.39±0.67	2.80±0.58	<0.001

Table 2. Mean± SD of pulmonary function tests, percentage of possible improvement and percentage change of FEV1 among young and elderly patients.

Groups / Variables	Young patients (n=82)	Elderly patients (n=56)	P value
FEV1, Lit	2.83±0.70	2.10±0.55	0.001<
FEV1, %pred.	84.1±15.8	77.36±15.83	0.013
Percentage change of FEV1 in males	75.05±46.61	71.39±41.30	0.721
Percentage change of FEV1 in females	100.79±51.34	69±37.39	0.015
Percentage of possible improvement of FEV1 in males	62.81±25.67	54.46±23.82	0.148
Percentage of possible improvement of FEV1 in females	78±24.04	63.58±41.24	0.087

DISCUSSION

The current study demonstrated that age does not affect bronchodilator response to treatment. In this study only percentage change of FEV1 in young females compared with elderly females was significant (p=0.015).In other words, elderly patients with severe persistent asthma did not show a significantly less response to bronchodilators when compared to young patients.

In another study, the age range of patients with acute asthmatic attack was about 30-35 years, and the average value of FEV1 was 30% predicted (18). In the present study, the baseline predictable FEV1 value at the same time was higher; it was 46% and 46.36% in young and elderly patients, respectively. This difference was related to the method of patient selection, because the studied subjects mostly referred to private clinics. In the current study, patients were divided into two groups: the young (age≤ 35 years), and the elderly (≥ 50 years). The cut-off age in our study was similar to the mean age of patients with acute asthma at presentation to the emergency room (9, 19-21).

The goals of asthma therapy in elderly patients are not different from those in younger asthmatic patients (22). The therapeutic approach for asthma in elderly patients does not differ from what is recommended for young patients. Although, the patho-physiologic mechanisms of asthma in the elderly are likely to be different from those seen in young asthmatic patients, and these differences might influence the clinical course and outcomes of asthma in this population. Moreover, characteristics and drug response in the elderly asthmatic patients differ from those seen in childhood asthma. Compared with younger cohorts, elderly asthmatic patients have a higher prevalence, and higher rates of bronchial hyper-reactivity, more severe asthma, and a lower prevalence of atopy. The symptoms of elderly asthmatic patients are more difficult to control with drug therapy, and these patients have steroid resistance and might respond better to leukotriene receptor antagonists compared with inhaled corticosteroids.

β-adrenergic agents are important medications for the acute and chronic management of asthma. Elderly patients with asthma might be less responsive to certain bronchodilators compared with younger patients (23,24). Anti-cholinergic and beta agonist agents are efficient in both young and old asthmatic patients, and generally age is not a predictor of response to either drug (8). In a study, Parker reported that beta-agonist responsiveness after methacholine-induced bronchoconstriction was similar in young and older subjects, and aging does not affect bronchodilator response to beta-agonist after methacholine-induced bronchoconstriction (10). Oosaki et al, from Japan reported that, in adult asthmatics the age of onset of asthma may not be related to the response to anti-asthmatic medications (25). Turner et al. reported that in young asthmatic children (age 3-9 years) the level of response to a bronchodilator increases significantly with increasing age (26).

Few large clinical studies have compared the results of asthma therapies in the elderly with the rest of the asthmatic population (27,28). Recently Haughney et al. in a randomized 6-month study showed that no difference in responses to budesonide/formoterol maintenance and reliever therapy was seen between the elderly and the younger patients (29). In their study Five-item Asthma Control Questionnaire (ACQ-5) scores improved equally in the two age groups (29).

In order to eliminate bias related to the degree of airway obstruction, we used the formula "percentage of possible improvement" to express the actual improvement. By using this formula, there was no significant difference between two age groups, in response to bronchodilator with respect to age. In this study, although the percentage changes of FEV1, in comparison with the baseline in young male and female asthmatic patients were higher than the changes in the elderly, only in the latter groups it was statistically significant (p=0.015). It must be mentioned that the baseline values of FEV1 in elderly patients are lesser than young subjects (1.28±0.38 lit vs. 1.57±0.47 lit). Various studies have indicated that improvement in pulmonary

function tests has a close association with the intensity of airflow obstruction **(**30,31). Accordingly, in our study the evaluation of method was based on calculation of the percentage of possible improvement in FEV1. Other researches had the same base **(**8,9). With this correction, there was no significant difference between the groups in terms of age.

Adrenergic responses suppress with aging, and old patients in comparison with young subjects need higher doses of isoproterenol or propranolol for regulation of heart rate (3). The elderly have reduced beta-adrenergic sensitivity to agonists, which is related to reduced beta-receptor affinity (6). Aging decreases responsiveness in several receptor systems, including the beta-adrenergic receptor system (7). The response to treatment with ipratropium and salbutamol is related to age. In a study by Ullah et al, it was reported that the response to salbutamol declined significantly with age, whereas response to ipratropium did not. In general, in patients aged less than 40 years salbutamol is the drug of choice. By advancing age, and the apparent decline of beta-adrenergic responsiveness, the initially comparatively small response to ipratropium becomes relatively more important and may predominate (5).

Aging results in changes in immune cell function that have been described for T-cells, macrophages, neutrophils, dendritic cells, and eosinophils. Peripheral blood eosinophils were isolated from younger (20-40 years old) and older (55-80 years old) subjects for in vitro functional assays. The eosinophil effector functions of degranulation and superoxide production were diminished in the older compared to younger asthmatic patients (32).

In young and old asthmatic patients with acute asthmatic attacks that received anti asthmatic drug, age did not play any role in evaluating the response to treatment, and only the percentage of possible improvement in FEV1 in males with acute asthma compared with elderly patients was statistically significant. It indicated that response to bronchodilator in acute asthma was not blunted in older patients in comparison with young ones.

We conclude that in severe persistent asthma age is not a predictor of response to treatment.

REFERENCES

1. Dow L, Carrol M. The aging lung: structural and functional aspects. In: Connolly M, ed. Respiratory disease in the elderly patient. London: Chapman and Hall Medical, 1996: 1-17
2. Vestal RE, Wood AJ, Shand DG. Reduced beta-adrenoceptor sensitivity in the elderly. *Clin Pharmacol Ther* 1979; 26 (2): 181- 6.
3. Barnes RF, Raskind M, Gumbrecht G, Halter JB. The effects of age on the plasma catecholamine response to mental stress in man. *J Clin Endocrinol Metab* 1982; 54 (1): 64- 9.
4. Bühler FR, Kiowski W, van Brummelen P, Amann FW, Bertel O, Landmann R, et al. Plasma catecholamines and cardiac, renal and peripheral vascular adrenoceptor-mediated responses in different age groups of normal and hypertensive subjects. *Clin Exp Hypertens* 1980; 2 (3- 4): 409-26.
5. Ullah MI, Newman GB, Saunders KB. Influence of age on response to ipratropium and salbutamol in asthma. *Thorax* 1981; 36 (7): 523- 9.
6. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJ. Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta-adrenergic sensitivity in the elderly. *N Engl J Med* 1984; 310 (13): 815- 9.
7. Feldman RD. Physiological and molecular correlates of age-related changes in the human beta-adrenergic receptor system. *Fed Proc*.1986; 45 (1): 48- 50.
8. Kradjan WA, Driesner NK, Abuan TH, Emmick G, Schoene RB. Effect of age on bronchodilator response. *Chest* 1992; 101 (6): 1545- 51.
9. Rodrigo G, Rodrigo C. Effect of age on bronchodilator response in acute severe asthma treatment. *Chest* 1997; 112 (1): 19- 23.
10. Parker AL. Aging does not affect beta-agonist responsiveness after methacholine-induced bronchoconstriction. *J Am Geriatr Soc* 2004; 52 (3): 388- 92.
11. Bellia V, Cibella F, Cuttitta G, Scichilone N, Mancuso G, Vignola AM, et al. Effect of age upon airway obstruction and

reversibility in adult patients with asthma. *Chest* 1998; 114 (5): 1336- 42.

12. van Schayck CP, Folgering H, Harbers H, Maas KL, van Weel C. Effects of allergy and age on responses to salbutamol and ipratropium bromide in moderate asthma and chronic bronchitis. *Thorax* 1991 May;46(5):355-9.
13. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152 (3): 1107- 36.
14. National Asthma Education and Prevention Program Expert Panel Report II: guidelines for the diagnosis and management of asthma. NIH Publication 97-4051. Bethesda, MD: National Institutes of Health; 1997
15. Williams SG, Schmidt DK, Redd SC, Storms W; National Asthma Education and Prevention Program. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. *MMWR Recomm Rep* 2003; 52 (RR- 6): 1- 8.
16. Weber RW, Petty WE, Nelson HS. Aerosolized terbutaline in asthmatics. Comparison of dosage strength, schedule, and method of administration. *J Allergy Clin Immunol* 1979; 63 (2): 116- 21.
17. Razi E, Moosavi GA. Serum total IgE levels and total eosinophil counts: relationship with treatment response in patients with acute asthma. *J Bras Pneumol* 2010; 36 (1): 23- 8.
18. Fanta CH, Israeal E, Sheffer AL. Managing and preventing severe asthma attack. *J Respir Dis* 1992; 13: 94-108.
19. Raimondi AC, Schottlender J, Lombardi D, Molfino NA. Treatment of acute severe asthma with inhaled albuterol delivered via jet nebulizer, metered dose inhaler with spacer, or dry powder. *Chest* 1997; 112 (1): 24- 8.
20. Colacone A, Afilalo M, Wolkove N, Kreisman H. A comparison of albuterol administered by metered dose inhaler (and holding chamber) or wet nebulizer in acute asthma. *Chest* 1993; 104 (3): 835- 41.
21. Rodrigo G, Rodrigo C. Assessment of the patient with acute asthma in the emergency department. A factor analytic study. *Chest* 1993; 104 (5): 1325- 8.
22. Braman SS, Hanania NA. Asthma in older adults. *Clin Chest Med* 2007; 28 (4): 685- 702, v.
23. Banerji A, Clark S, Afilalo M, Blanda MP, Cydulka RK, Camargo CA Jr. Prospective multicenter study of acute asthma in younger versus older adults presenting to the emergency department. *J Am Geriatr Soc* 2006; 54 (1): 48- 55.
24. Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Impaired bronchodilator response to albuterol in healthy elderly men and women. *Chest* 1995; 108 (2): 401- 6.
25. Oosaki R, Mizushima Y, Kawasaki A, Kashii T, Kobayashi M. No significant effect of age of onset on response to anti-asthmatic medications in adult asthmatics. *In Vivo* 1996; 10 (3): 377- 82.
26. Turner DJ, Landau LI, LeSouëf PN. The effect of age on bronchodilator responsiveness. *Pediatr Pulmonol* 1993; 15 (2): 98- 104.
27. King MJ, Hanania NA. Asthma in the elderly: current knowledge and future directions. *Curr Opin Pulm Med* 2010; 16 (1): 55- 9.
28. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31 (1): 143- 78.
29. Haughney J, Aubier M, Jørgensen L, Ostinelli J, Selroos O, van Schayck CP, et al. Comparing asthma treatment in elderly versus younger patients. *Respir Med* 2011; 105 (6): 838- 45.
30. Rebuck AS, Chapman KR, Abboud R, Pare PD, Kreisman H, Wolkove N, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987; 82 (1): 59- 64.
31. Braun SR, McKenzie WN, Copeland C, Knight L, Ellersieck M. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease. *Arch Intern Med* 1989; 149 (3): 544- 7.
32. Mathur SK, Schwantes EA, Jarjour NN, Busse WW. Age-related changes in eosinophil function in human subjects. *Chest* 2008; 133 (2): 412- 9.