Review Article

β –Blockers in reactive airway disease

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ABSTRACT

Beta-2- adrenergic agonists agonists are used in the treatment of reversible airway disease. β-blockers, due to their bronchoconstrictor effects, are supposed to be deleterious in such patients. In this review, we are putting forth some recent studies and meta analysis, which indicate that the chronic use of β-blockers in patients with reversible airway disease does not produce pulmonary impairment. Also, these drugs need not be withheld from patients with other diseases like hypertension, after weighing the risk: benefit ratio.

Key Words : β- blockers, COPD, Asthma

KEY MESSAGES: β- blockers are no longer absolute contraindications in patients with reactive airway disease. Various studies and metaanalysis now show that this group of drugs can be safely used and they have more so shown benefits in the subgroup of the population with concomitant cardiovascular and airway diseases.

INTRODUCTION

Paradoxical pharmacology is now well established for the management of certain clinical conditions like the use of β-blockers in congestive heart failure[1] and the use of methylphenidate or amphetamine to treat hyperactivity in children.[2] To understand the potential role of β blockers in the management of reactive airway diseases, we reviewed the current body of evidence that exists in the form of animal and human studies.

Reactive airway disease is defined as bronchial asthma or chronic obstructive pulmonary disease (COPD) with a reversible obstructive component.[3] Asthma is characterized clinically by recurrent bouts of coughing, shortness of breath, chest tightness, and wheezing; physiologically by a widespread, reversible narrowing of the bronchial airways and by a marked increase in the bronchial responsiveness to inhaled stimuli; and pathologically by the lymphocytic, eosinophilic inflammation of the bronchial mucosa.[4] Chronic obstructive pulmonary disease (COPD) has been defined as a disease state which is characterized by an airflow limitation that is not fully reversible. It includes emphysema which is characterized by the destruction and the enlargement of the lung alveoli; chronic bronchitis which includes chronic cough and phlegm and by the small airways disease in which the small bronchioles are narrow.[5]

In the airway smooth muscles, there is a balance between the sympathetic activity which produces bronchodilation and the parasympathetic activity which produces bronchoconstriction. Selective β 2-agonists are widely used for treatment of asthma and COPD due to their potent bronchodilatory action. However, the control of bronchial asthma worsens when β-agonists are inhaled regularly, as they confer no significant benefit on the lung function, but on the contrary, they may have a deleterious effect. [6] The bronchoprotective effect of the long-acting β-agonists i.e., their inhibition of exercise-induced bronchoconstriction rapidly wanes with regular use, a paradoxical effect that has not been fully explained.

The β adrenoreceptor antagonists which are also known as β-blockers, are contraindicated in patients of bronchial asthma, because they can induce bronchoconstriction on acute dosing. However, chronic treatment has shown a decrease in the airway hyperresponsiveness. The hypothesis that the bronchospasm which is caused by the β-blockers is due to the competitive antagonism of the β2-adrenoreceptors (β2-AR) which in turn prevents bronchodilation by the endogenous catecholamines, is not consistent with the finding that significant levels of β2- receptor antagonism can be achieved without an accompanying decrease in the airway diameter.[7] There is also no evidence to support that mast cell degranulation occurs following the acute administration of β-blockers, as might be anticipated if the endogenous catecholamines were suppressing mast cell function.[8]

ANIMAL STUDIES

The airway epithelium contains a large number of goblet cells which are filled with mucus, which protects the underlying tissue from the external environment[9]. These cells are increased in numbers in asthma and contribute to the airflow obstruction[10]. Acute treatment with the β blockers is accompanied by the worsening of the airway hyperresponsiveness (AHR) in sensitized and challenged mice, while chronic treatment for 28 days showed a protective effect on the airway responsiveness to methacholine.[11] The authors found that the chronic administration of carvedilol or nadolol increases the number of membrane associated β-ARs and that it is this change in the receptor number that results in the bronchoprotection against spasmogens.[11] A study which was conducted in the murine model of asthma revealed that β2-AR signaling was required for the full development of the three

Study by authors	Year of study	Conclusions
ANIMAL STUDIES		
Nguyen LP etal[9]	2009	β- blockers attenuate asthma like phenotype
Nguyen LPetal[10]	2008	β- blockers reduce the inflammatory cells in bronchoalveolar lavage
Callaerts- Vegh Z etal[11]	2004	Protective effect on airway responsiveness to methacholine
De Clerck F et al[12]	1989	Nebivolol did not increase pulmonary reactivity
CLINICAL STUDIES		
Rulten FH etal[30]	2010	β- blockers reduce mortality and exacerbations in COPD
Hanania NA etal[13]	2008	Nadolol decreased airway hyperresponsiveness to methacholine
Van Gestel YRBM etal[31]	2008	Cardioselective β-blockers reduce mortality in COPD patients undergoing surgery
Salpeter SRetal[14]	Cochrane Review 2005	Cardioselective -blockers produce no change in FEV1
Cazzola M eta[21]	2005	Airway obstruction control was similar with nebivolol and nifedipine
Camsari Aetal[24]	2003	Cardioselective β-blocker in CAD and COPD did not produce any adverse effect
Clauge HWetal[15]	1984	COPD patients resistant to airway obstruction by β-blockers

[Table/Fig-1]: Studies favouring the use of - blockers in airway disease

cardinal features of asthma, namely; mucosal metaplasia, airway hyperresponsiveness and inflammatory infiltration into the lungs. [9] In these experiments, genetic and pharmacological strategies to examine the effects of the β2-AR blockade were used. It was found that the chronic blockade of these receptors by an inverse agonist like nadolol, produced the attenuation of asthma –like the phenotype in the murine antigen derived model of mice. It has been suggested that two β blockers i.e. nadolol and ICI 118551 reduced the inflammatory cells in the bronchoalveolar lavage of antigen challenged mice. In addition, nadolol also reduced the levels of the cytokines, IL-13, IL-10, IL-5, and TGF-β1. Also, chronic treatment with the β blockers produced a marked, time dependent decrease in the goblet cell and mucin content of the airway epithelium.[10] However, β blockers have shown differential effects on different organs e.g. nebivolol significantly reduced heart rate without significantly increasing the pulmonary reactivity in guinea pigs.[12]

HUMAN STUDIES

In human studies, it has been shown that chronic treatment with the β blockers does not cause pulmonary impairment. In a pilot study, a non selective β blocker like nadolol, which was administered to ten patients of asthma, resulted in more than a 10% fall in FEV1 after the first dose in four subjects. However, on using the escalating strategy for nine weeks, the drug was well tolerated and produced a dose dependent decrease in AHR to methacholine in most of the subjects.[13] The limitations of this study were its small sample size and the inclusion of patients with mild disease. Another meta-analysis of 20 homogeneous randomized controlled trials on the use of cardioselective β-blockers in patients with COPD, demonstrated that these agents, when given as a single dose for a long duration, produced no change in FEV1 or in the respiratory symptoms as compared to placebo. The findings remained unchanged in the subgroup analyses of the subjects with severe COPD.[14] Another study revealed that patients with poorly reversible COPD were resistant to the airway obstruction which was caused by the β- blockers. However, the β blockers which were used in this study had an intrinsic sympathomimetic activity and the parameters which were measured were wheezing and a fall in FEV1 to > 30%.[15] Comparison of a single oral dose of nebivolol and celiprolol revealed that there was a slight decrease in FEV1, but that none of the drugs impaired the lung functions in patients with mild asthma.[16]

On the contrary, some studies recommend a cautious use of β-blockers in airway diseases. A study by van der Woude HJ etal, which was done to determine the effects of celiprolol, propranolol and metoprolol on FEV1 and airway hyperresponsiveness, found that propranolol reduced FEV1 and the bronchodilating effect of formeterol. Metoprolol and propranolol increased the airway hyperresponsiveness, whereas celiprolol did not have any pulmonary effects.[17]Despite having a β2 sparing effect, celiprolol and metoprolol differed in their effects on AHR and the effect which was shown by metoprolol resembled that of propranolol. Thus, a property other than the β- receptor selectivity is involved in the increase in AHR in patients with COPD. Hence, it was demonstrated that the pulmonary effects of different β- blockers vary. Another study on 13 patients with COPD revealed that the pulmonary functions worsened with the orally administered non selective β- blocker, propranolol. The authors recommend that the serial measurement of the pulmonary functions should be done as a therapeutic guide to detect progressive deterioration[18].

It has been found in a study, that 28% of the 270 patients who were discharged from a university hospital after an acute exacerbation of COPD, were suffering from hypertension.[19] β- blockers are valuable agents in the treatment of hypertension. They must be used with extreme care in patients with asthma.[20] A pilot study comparing nebivolol and nifedipine in patients with hypertension showed that both agents produced a similar and significant reduction in the blood pressure. FEV1 was decreased non-significantly in the nifedipine group and slightly in the nebivolol group. However, the day to day airway obstruction control was similar in both the groups.[21] Even the American College of Chest Physicians recommends that the application of a new class of α-β blockers with an β- blocking activity in hypertensive patients with compromised pulmonary function, is warranted.[22] In patients with concomitant COPD and heart failure, Recio-Iglesias J etal found that the β-blocker use was determined by LVEF without any relationship to the severity of COPD.[23] Camsari and his colleagues did not come across any side effect which could be attributed to metoprolol in 50 patients with coronary heart disease and COPD.[24]

DISCUSSION

The hypothesis regarding the role of the chronic use of β-blockers in bronchial asthma started as a theoretical concept, but later,

animal studies showed some positive results. This was followed by human studies, some of which have shown encouraging results. Some authors are of the opinion that prescribing selective β blockers, particularly those with an intrinsic sympathomimetic activity, in patients with stable mild to moderate asthma, appears to be safe.[25] The intrinsic sympathomimetic activity in part will stimulate the β-receptors as well.[26]

Beta blockers do not impair the health status in patients with co-existing COPD. In view of the life preserving effects in patients with cardiovascular disease, it has been suggested that β blockers can in most circumstances, be judiciously administered in patients with COPD.[27]. The diminished use of β blockers in patients with COPD is of concern, considering that many patients with COPD ultimately die of cardiovascular causes and in particular, ischaemic heart disease.[28] There is little evidence that serious harm occurs secondarily on the use of cardioselective agents, when given carefully under specialist supervision and at low doses.[29] A recent study suggested that the use of β blockers may reduce mortality as well as the risk of exacerbations of COPD, in patients with COPD with concurrent cardiovascular disease. [30]Cardioselective β-blockers reduced long term mortality in patients with COPD, who underwent major vascular surgery.[31] Intensified dosing regimens appeared to be superior to low doses in terms of their impact on a 30-day mortality.[31]

In conclusion, it appears safe to prescribe cardioselective beta-blockers in mild to moderate reversible airway diseases under medical supervision. Keeping in mind the benefits of beta blockers in conditions like heart failure and hypertension, these agents should not be withheld from such patients. Current evidence suggests that giving beta-blockers to patients with coronary artery disease and chronic obstructive pulmonary disease (COPD) or asthma lowers the 1-year mortality rate to a degree which is similar to that in patients without COPD or asthma, without worsening the respiratory function[32]. However, long term trials are needed to establish their safe use in these comorbidities.

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DECLARATION ON COMPETING INTERESTS: No competing Interests.

Date of Submission: **Nov 26, 2010**
Date of Peer Review: **Jan 25, 2011**
Date of acceptance: **Feb 19, 2011**
Date of Publication: **Apr 11, 2011**