REVIEW

Beta-blockers: friend or foe in asthma?

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Background and aim: Recently, β-blockers have been suggested as a potential maintenance treatment option for asthma. The aim of this review is to provide an overview of the current knowledge of the potential benefits and risks of β-blocker therapy for asthma.

Method: Systematic literature review.

Results: No significant increase in the number of patients requiring rescue oral corticosteroid for an exacerbation of asthma has been observed after initiation of β-blocker treatment. Patients with mild to moderate reactive airway disease, probably both asthma and chronic obstructive pulmonary disease, may have a limited fall in forced expiratory volume in 1 second (FEV_1) following single-dose administration of β-blocker, whereas no change in FEV_1 has been reported following long-term administration. In a murine model of asthma, long-term administration of β-blockers resulted in a decrease in airway hyperresponsiveness, suggesting an anti-inflammatory effect. In keeping with this, long-term administration of a nonselective β-blocker to steroid-naïve asthma patients has shown a dose-dependent improvement in airway hyperresponsiveness, and either an asymptomatic fall in FEV_1 or no significant change in FEV_1. Furthermore, available studies show that bronchoconstriction induced by inhaled methacholine is reversed by salbutamol in patients on regular therapy with a β-blocker. On the other hand, a recent placebo-controlled trial of propranolol and tiotropium bromide added to inhaled corticosteroids revealed no effect on airway hyperresponsiveness and a small, not statistically significant, fall in FEV_1 in patients classified as having mild to moderate asthma.

Conclusion: The available, although limited, evidence suggests that a dose-escalating model of β-blocker therapy to patients with asthma is well tolerated, does not induce acute bronchoconstriction, and, not least, may have beneficial effects on airway inflammation and airway hyperresponsiveness in some patients with asthma. Further studies addressing the potential role of β-blocker therapy for asthma are clearly needed, but careful selection of the target population is warranted.

Keywords: asthma, beta-blockers, lung function, airway responsiveness

Introduction

Short-acting β_2-agonists (SABA) have been recommended for acute relief of asthma symptoms for decades,[1] and long-acting β_2-agonists (LABA) are used as add-ons to inhaled corticosteroids (ICS) for patients not achieving asthma control on low-dose therapy with inhaled corticosteroids.[1] β_2-agonists are hence, together with ICS, the most commonly used drugs in the pharmacological management of asthma.[1]

It has been reported that chronic use of both SABA and LABA in asthma is associated with development of tolerance, an increase in airway hyperresponsiveness, poor asthma control, and even an increase in asthma mortality.[2,3] Postmarketing studies

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were therefore initiated in order to clarify the safety of using LABA as maintenance therapy for patients with asthma.[4,5] Although the Salmeterol Multicenter Asthma Research Trial[4] and the Serevent Nationwide Surveillance Study[5] have been much debated, not least with regard to the safety issue, they have added to the current recommendation that LABA should only be used as add-on therapy for patients not achieving disease control on ICS as monotherapy.[1] However, on the basis of available studies, a potential risk of serious adverse events cannot be completely excluded when LABA is used as an add-on to ICS in patients with asthma. It is hoped that the ongoing safety studies will provide an answer to this question.

In contrast to β-agonists, β-blockers have for many years been regarded as contraindicated in patients suffering from asthma due to the potential risk of triggering bronchoconstriction,[6,7] which could potentially result in an insufficient response to bronchodilator therapy during a severe asthma attack. Although not as common as in patients with chronic obstructive pulmonary disease (COPD), especially elderly patients with asthma who may have comorbidities such as chronic heart failure and angina, use of β-blockers is known to have symptomatic effect and to improve the outcome.[8] Few studies have examined the risk–benefit ratio of maintenance therapy with β-blockers in patients with asthma,[9] and the present contraindication is, therefore, based solely on the risk for bronchoconstriction after acute administration. There have been reports of severe attacks of asthma triggered by a single dose of β-blockers.[10,11] However, some researchers have, in line with the positive effect of β-blockers in patients with left ventricular failure, suggested that β-blockers may also have a beneficial effect in asthma.[6] This suggestion has probably at least partly been based on the observations of potential serious adverse effects of LABA therapy for patients with asthma.[4,5]

The density of β-receptors in airway smooth muscle does not change at different airway levels, so bronchioles have a similar density to large airways, but β-receptors are also expressed on other potentially important target cells, including airway epithelium, mast cells, type 2 pneumocytes, submucosal glands, and postcapillary venules. Furthermore, inflammatory cells, including eosinophils and neutrophils, also express β-receptors, which are rapidly desensitized by β-agonists. The effects of β-blockers in asthma, whether beneficial or detrimental, may therefore be mediated through several potential pathways.

The aim of this short review is to provide the reader with an overview of our current knowledge of the potential risks and beneficial effects of β-blockers in the management of asthma.

Methods

A series of searches, last updated in May 2013, was carried out using the PubMed database. The search strategy was intended to be broad, in order to maximize the capture of citations for peer-reviewed publications relevant to asthma and β-blockers. The PubMed searches were carried out using the following algorithm of MeSH terms: asthma, asthma-like symptoms and β-blockers or β-blockade; the searches were repeated with these terms in combination with reactive airways disease and reversible airway disease. The citation pool was further supplemented from manual assessment of the reference lists accompanying original research and other systematic reviews of aspects related to asthma and β-blockers and from other publications identified as being relevant for further review. Only publications in English published after 1985 reporting original research (ie, animal models or studies of humans) assessing potential risks and benefits of β-blocker therapy in asthma were included in this review. Studies evaluating the effect of β-blocker therapy in patients with COPD only were excluded, primarily because the risk–benefit ratio of β-blocker therapy differs substantially between patients with asthma and patients with COPD due to differences in the prevalence of comorbidities, including cardiovascular disease.

Results
The potential risks associated with administration of β-blockers to asthma patients

In an observational study, Morales et al[7] assessed the possible association between prescription of β-blockers to asthma patients and the incidence of severe asthma exacerbations requiring treatment with oral corticosteroids. The primary aim was to determine whether the first β-blocker prescription was associated with a subsequent prescription of a rescue course of oral corticosteroids. Clinical data were obtained from one third of all Scottish general practices, with 1.76 million registered patients. Patients with asthma were identified on March 31, 2007 and data on all asthma-related medication within the preceding 2 years were recorded. Data on all patients with a read code (hierarchical clinical coding system used in the UK; also necessary for reimbursement claims) for asthma as well as patients aged 18–40 years were extracted. An asthma case was defined as an individual with the combination of asthma READ code and no READ code for COPD. In order

to avoid inclusion of individuals with undiagnosed COPD, the researchers only included patients aged >40 years if they were registered as "never smokers." A total of 53,944 adults with asthma were identified, of whom 1,527 patients had had a prescription for a β-blocker (both nonselective and cardioselective β-blockers). The cohort of interest comprised the 695 patients receiving the first β-blocker prescription during the study period. A new oral β-blocker prescription was defined as the first β-blocker prescription with a pre-exposure period of ≥84 days. Active asthma was defined as prescriptions of asthma-related medications, including SABA, LABA, ICS, fixed-combination inhalers (LABA/ICS), theophylline, and leukotriene antagonists, filled between January 1, 2005 and the date of the new β-blocker prescription. Patients were required to have a follow-up period of at least 84 days to determine the potential effects of β-blocker therapy on incidence of prescribed rescue courses of oral corticosteroid. Patients receiving nonselective β-blockers were younger (<40 years of age) and more likely to be women. Patients prescribed selective β-blockers were more likely to have congestive heart failure and ischemic heart disease. For the 599 patients receiving a new β-blocker prescription, asthma severity was defined according to the British Thoracic Society guidelines.[12] Of these 599 patients, 376 (62.8%) were prescribed SABA, 274 (45.7%) were prescribed ICS, and 70 (11.7%) were prescribed LABA/ICS prior to the first β-blocker prescription. Of 441 patients identified as having active asthma, 367 had the required follow-up period and were therefore included in the final analysis. The use of rescue steroids was quantified at baseline, for weeks 0–2, for weeks 2–4, and for weeks 4–8. The final analysis revealed no statistical difference in the proportion of patients prescribed oral steroids in the weeks following the first β-blocker prescription. The authors concluded that no large increase was observed in number of patients requiring oral corticosteroids for exacerbation of asthma during the first, possibly most critical, period after the initiation of β-blocker treatment, although a small increase in risk could not be excluded.

Van Zyl et al[13] studied the effects of two cardioselective β-blockers, ie, celiprolol and atenolol, on respiratory function and asthma control in patients with asthma and concomitant mild to moderate essential hypertension. In contrast to atenolol, celiprolol is claimed to have bronchodilator properties. Patients were eligible for the study provided they had a forced expiratory volume in 1 second (FEV_1) <85% predicted combined with either a 15% increase in FEV_1 in response to salbutamol or a positive histamine challenge test (defined as a PC_{20} [the provocative dose causing a 20% fall

in FEV_1] histamine <8 mg/mL). After a single-blind 2-week run-in period, the enrolled patients (n = 12) were randomized in a double-blind placebo-controlled design to either 100 mg atenolol or 400 mg celiprolol daily or vice versa for 4 weeks, with a 2-week washout period in between. Spirometry was performed prior to the first dose of trial medication (celiprolol, atenolol, or placebo), and postdose spirometry was done at the following time points: 30 minutes, 1 hour, 2 hours, and 3 hours. At 3 hours, all patients were given a single dose of inhaled salbutamol, and spirometry was repeated after 5–15 minutes. Patients recorded symptom scores and use of inhaler medication throughout the study period. Ten of 12 patients completed the study; one patient had an acute exacerbation during the study period and one patient required add-on antihypertensive therapy. A progressive fall in FEV_1 and forced vital capacity was observed during the 3 hours after the single-dose challenge with atenolol, followed by an improvement to prechallenge levels after administration of salbutamol. In contrast to this, both FEV_1 and forced vital capacity remained unchanged after single-dose administration of celiprolol, whereas the response to salbutamol was preserved. The single-dose response after 2 weeks of maintenance β-blocker therapy was similar to the response observed after placebo. No effects of β-blocker therapy were observed on symptom scores or use of rescue bronchodilator. On the basis of the difference in response to the two bronchodilators, the authors concluded celiprolol may have a more favorable safety profile than atenolol in patients with asthma. Although this study revealed a β-blocker–associated fall in lung function and no effect of maintenance therapy on asthma control, it should be noted that information on mean level of lung function and smoking habits was not provided. Inclusion of patients with COPD who met the inclusion criteria primarily due to a low baseline level of lung function is, therefore, a possibility, which may compromise the interpretation of the findings. Similarly, Yamakage et al[14] included patients (mean age 59.8 years) with at least two coronary risk factors, airway resistance >180% predicted and FEV_1 <70% predicted, in a study investigating the effects of esmolol and landiolol on wheezing during induction of anesthesia.

In a double-blind, randomized, crossover study, Wilcox et al[15] investigated the effect of metoprolol and bevantolol in 16 patients with asthma. Cumulative doses, ie, 12.5 mg, 25 mg, 50 mg, and 100 mg of metoprolol or 18.75 mg, 37.5 mg, 75 mg, and 150 mg of bevantolol, were administered at 2-hour intervals. Symptoms and lung function were monitored, and treatment was stopped if significant symptoms or a 20% decline in FEV_1 were observed.

The cumulative dosing regimen in general proved to be a safe and effective means of assessing bronchial responsiveness to β-blockers in asthma, but one patient had to be withdrawn after the first dose due to severe bronchoconstriction. Of the 15 patients exposed to both β-blockers, seven patients were withdrawn prematurely. The maximum tolerated cumulative dose of metoprolol and bevantolol was 26.8 mg and 45.5 mg, respectively, doses much lower than usually required for therapeutic activity. The authors concluded that even in patients who tolerate single doses of β-blockers, the response to repeated treatment is unpredictable and, therefore, that β-blocker therapy should be avoided in patients with asthma.

Potential benefits of β-blockers for patients with asthma
Animal studies
Observations by Callaerts-Vegh et al[16] from a murine model of asthma have shown that, although acute administration of β-blockers increased the level of airway hyperresponsiveness, longer-term administration (28 days) resulted in a decrease in airway hyperresponsiveness. Furthermore, this study also showed that chronic therapy reduced the total cell count in bronchoalveolar lavage (BAL) fluid, BAL eosinophil counts, and BAL cytokine levels, including interleukin (IL)-5, IL-10, and IL-13. Treatment with a β-blocker for 28 days also decreased mucin content and partially reversed the pathological changes in the airway epithelium.[17,18]

Human studies
Bauer et al[19] studied the effects of an oral osmotic formulation of metoprolol and atenolol on skeletal muscles and bronchial smooth muscles. They included 28 patients with stable asthma and concomitant essential hypertension, but no other comorbidities. Patients were included if they had a FEV_1 >50% predicted, an increase in FEV_1 >15% after administration of 400 μg salbutamol, and a diastolic blood pressure >90 mmHg. The electrocardiogram and chest X-ray were normal in all patients. The study was a randomized, double-blind, three-period, crossover, placebo-controlled trial with at least a 7-day washout phase between treatment periods. The study drugs were administered once daily in all treatment periods. On treatment days 1 and 7, FEV_1, specific airway conductance, finger tremor, blood pressure, and heart rate were measured. Dose-response curves were then constructed using six increasing doses of inhaled salbutamol, as follows: 12.5 μg, 25 μg, 75 μg, 300 μg, 400 μg, and 800 μg, dose increments were made at

20-minute intervals, and a 5-minute period was scheduled for recording all parameters. A total of 18 patients completed the study and were included in the analyses. Ten patients were excluded: six withdrew for personal reasons, one had an upper respiratory tract infection, one experienced finger tremor and palpitations of moderate degree during the salbutamol dose response challenge while on placebo therapy (day 1) and declined to continue, and two experienced a worsening of their asthma (one patient after having finished the placebo and metoprolol treatment period and one after the metoprolol and atenolol phase). No statistically significant differences in baseline characteristics were found between the ten patients excluded and the 18 patients who completed the study. The study showed that a single dose (day 1) of both metoprolol and atenolol had no measurable influence on bronchial β_2-adrenergic receptors as assessed by the salbutamol dose-response curve in hypertensive asthma patients. Neither metoprolol nor atenolol caused a difference in postmedication (after 30 minutes of rest) baseline lung function before administration of salbutamol, and the salbutamol dose-response curves obtained after active treatment were indistinguishable from those obtained after placebo. Multiple doses of metoprolol caused no measurable bronchial β_2-adrenergic receptor antagonism in the patients, whereas multiple doses of atenolol caused a significant shift to the right in the salbutamol dose-response curve. No significant influence was reported on bronchomotor tone in hypertensive asthma patients when treated with either single or multiple doses of metoprolol, although multiple dosing did cause blockade on β_2-adrenergic receptors of skeletal muscle. The authors concluded that metoprolol had no measurable influence on bronchomotor tone; nonetheless, other side effects and risks could arise when β-blockers are administered to asthma patients.

In a pilot study, Hanania et al[3] recruited ten steroid-naïve patients with asthma into a prospective open-label, dose-escalating study investigating the safety of the nonselective β-blocker nadolol. All participants fulfilled the following criteria: (1) diagnosed with asthma, (2) aged 18–50 years, (3) non-smokers or past smokers with a history of <10 pack years, (4) baseline prebronchodilator FEV_1 ≥ 80% of predicted value, PC_{20} <8 mg/mL methacholine, and (6) baseline blood pressure ≥110/70 mmHg and pulse rate ≥60 beats per minute. Patients were not eligible for the study if they had other significant health issues and/or had been using any controller medication for asthma within 4 weeks of baseline. The patients were followed for 11 weeks and received medication (nadolol) for 9 weeks. After a 2-week run-in period, eligible patients were

entered into a dose-escalating phase lasting up to 6 weeks and then into a 3-week period on stable dose. The initial dose was 10 mg once daily and it was escalated, maintained, or reduced every week at the study visits on the basis of predetermined criteria, including level of lung function. All participants completed the study and tolerated a maximum nadolol dose of 10 mg (n = 3), 20 mg (n = 4), or 40 mg (n = 3). The study showed a dose-dependent improvement in PC_{20} methacholine in eight of ten patients and a 5%, statistically significant, decrease in FEV_1. The decline in FEV_1 was asymptomatic, and there was no significant correlation between the maximum dose of nadolol tolerated and the fall in FEV_1. The study indicates that treatment of asthma patients with a nonselective β-blocker, nadolol, is well-tolerated and actually may have a beneficial effect when repeated daily doses are administered in patients with mild asthma not on controller medication.

Hanania et al[20] completed another open-label study of chronic treatment with nadolol, also in patients with mild asthma not on controller therapy. The study comprised ten patients, used a dose-escalating model, and was 13 weeks long, including at least three weeks on the final tolerated dose. The initial dose of 1.25 mg was escalated biweekly depending on predetermined criteria, ie, lung function, asthma control, and hemodynamic parameters. Seven of the ten patients tolerated a maximum dose of 40 mg; one tolerated a daily dose of 10 mg and one a daily dose of 5 mg. One participant was excluded from the study because of an asthma exacerbation while being treated with the minimal dose of 1.25 mg. Results indicated a significant effect on airway hyperresponsiveness and no significant changes in FEV_1. In participants from both studies by Hanania et al[3,20] (n = 18), bronchodilator responsiveness to salbutamol was evaluated immediately after the methacholine challenge test at the final visit. Spirometry performed 20 minutes after administration of salbutamol showed that salbutamol reversed the methacholine-induced bronchospasm in all nadolol-treated patients. This is similar to observations in patients with asthma and no history of treatment with β-blockers, for whom administration of salbutamol after methacholine challenge led to a faster recovery of FEV_1 compared with placebo.[21] The former findings, therefore, suggest that β-blocker therapy does not inhibit the bronchodilating effect of salbutamol.

In keeping with this, Short et al[22] investigated the safety of acute exposure to propranolol in patients with asthma challenged with histamine in order to mimic an asthma exacerbation, and observed that nebulized salbutamol and ipratropium bromide produced a full recovery of bronchoconstriction induced by propranolol and histamine.

In a very recent double-blind, placebo-controlled crossover study, Short et al[23] assessed the effect of the nonselective β-blocker propranolol as add-on to ICS in adults with asthma. A total of 18 patients classified as having mild to moderate asthma based on level of lung function (mean FEV_1 93% predicted) and prescribed medium dose of ICS (mean daily dose 440 µg) completed the study. The study protocol consisted of a 6–8-week dose titration of propranolol or placebo as tolerated by the individual participants, up to a maximum daily dose of 80 mg; the primary outcome variable was airway responsiveness to inhaled methacholine. Apart from add-on propranolol or placebo, all participants were also treated with tiotropium bromide once daily for the first 4–6 weeks of each treatment period. The treatment response was also evaluated by histamine responsiveness, lung function, and questionnaires (Mini Asthma Quality Of Life Questionnaire and Asthma Control Questionnaire). No effect of propranolol versus placebo was observed on airway responsiveness to methacholine ($P = 0.89$), and likewise no difference was reported in histamine responsiveness or responses to the questionnaires. However, a small but statistically significant decrease in salbutamol responsiveness after the histamine challenge test was observed (mean difference in FEV_1 5.3% of the predicted value), and a small decline in FEV_1 was also observed at the end of the propranolol treatment period. Apart from not supporting the concept of β-blocker therapy in asthma, this small negative controlled trial may have important implications for possible future trials in relation to the target population, duration of therapy, and concurrent treatment with long-acting bronchodilators.

Discussion

Initiation of β-blocker treatment for diseases other than asthma is not associated with an increase in the need for rescue courses of oral corticosteroid for an exacerbation of asthma.[7] However, patients with mild to moderate reactive airway disease, in most studies likely including both asthma and COPD, may have a limited decrease in FEV_1 after single-dose administration of β-blocker, whereas no change in FEV_1 has been reported after long-term administration.[9] Also reassuring is the observation by Hanania et al[3,20] that asthma patients treated with β-blockers have a preserved and sufficient response to bronchodilators. Even though a potential risk cannot be ruled out and the intraindividual variation should be remembered, the available studies suggest that chronic use of cardioselective β-blockers, at least, is well-tolerated in asthma patients.

On the other hand, evidence from both human and animal studies has revealed positive effects on airway hyperresponsiveness and a probable anti-inflammatory effect with the chronic use of β-blockers.[3,16,20] However, the very recent randomized placebo-controlled study by Short et al[23] revealed no positive effect of treatment with a nonselective β-blocker on airway responsiveness to methacholine or histamine, lung function, and symptoms in patients with mild to moderate asthma (mean FEV_1 93% predicted) treated with medium-dose ICS. The study by Short et al,[23] although not lending support to the concept of a positive effect of β-blockers in asthma, may suggest that future controlled trials addressing this question should perhaps include patients with more severe asthma. This would be in keeping with the reported positive effects of β-blocker therapy for patients with heart failure. It is well documented that obese individuals not only have a high prevalence of asthma, but also have less-favorable response to current recommended asthma therapy.[24] One of the possible mechanisms underlying the association between obesity and asthma may be increased stiffness of airway smooth muscle,[25] and obese patients with asthma might, therefore, also be a target group in future trials of β-blocker therapy for asthma. Furthermore, in the study by Short et al,[23] patients were treated with add-on tiotropium bromide for most of the study period. Recent studies in patients with asthma suggest that tiotropium may have important anti-inflammatory effects,[26] and adding tiotropium to the treatment regimen in the study by Short et al[23] may, therefore, have blunted the effect of the primary intervention.

The observations in currently available studies, although limited, clearly suggest that large-scale clinical trials, probably using a dose-escalating model, are needed in order to explore the potential positive effect of chronic treatment with β-blockers in patients with asthma, including patients with more severe asthma.

Disclosure

The authors report no conflicts of interest in this work.

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