

CO-MORBIDITIES

Cardioselective Beta-Blocker Treatment of Hypertension in Patients with Asthma: When Do Benefits Outweigh Risks?

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Background. Benefits outweigh risks of cardioselective beta-blocker therapy in patients with nonsevere asthma and a history of heart failure or myocardial infarction (MI). This review summarizes the risks versus benefits of using cardioselective beta-blockers in the treatment of hypertension in patients with asthma. **Methods.** We searched the English literature from 1976 to 2011 via PubMed, EMBASE, and SCOPUS using the following search terms: “beta-blocker treatment of hypertension” AND “asthma”; “cardioselective beta-blockers” AND “asthma.” When pertinent articles were found, we assessed relevant articles cited in those papers. All studies related to cardioselective beta-blocker use in patients with asthma and hypertension were included. **Results.** Seven studies with patient populations ranging from 10 to 17 patients evaluated cardioselective beta-blockers in patients with asthma and hypertension. Atenolol and/or immediate-release metoprolol were evaluated in these studies. The duration of beta-blocker therapy in four studies was 1–8 weeks; two studies were single dose and one investigation lasted 8 months. Metoprolol and atenolol were generally well tolerated except at higher doses such as metoprolol >100 mg daily. **Conclusion.** In the absence of concomitant cardiovascular disease, routine use of beta-blockers for the treatment of hypertension in patients with asthma should be avoided

Keywords asthma, cardioselective beta-blockers, hypertension

INTRODUCTION

It is estimated that 76.4 million Americans have hypertension, and at least 22 million Americans, including over 16 million adults, have asthma (1, 2). Therefore, it is obvious that a very large number of patients will likely have both hypertension and asthma. Evidence to date supports that benefits outweigh risks of *cardioselective* beta-blocker therapy in patients with asthma after myocardial infarction (MI) or for the long-term management of heart failure (2–6). The use of cardioselective beta-blockers in patients with hypertension and asthma has also been encouraged (3, 4). Because of the wide array of antihypertensive agents available, it is logical to question the routine use of cardioselective beta-blockers in patients with the dual diagnoses of hypertension and asthma. In addition, the role of beta-blockers as first-line treatment in the long-term management of high blood pressure is undergoing reassessment (7, 8). Salpeter et al. (4) point out that long-term safety of cardioselective beta-blockers, especially during acute asthma exacerbations needs to be established. Noncardioselective beta-blockers should be avoided in patients with asthma, and no beta-blockers should be initiated in patients with severe asthma (2–6).

The purpose of this review is to assess the benefits versus risks of using cardioselective beta-blockers in patients with asthma and hypertension. Real-world examples are given of patients with asthma and high blood

pressure who would benefit most from cardioselective beta-blocker therapy.

METHODS

We searched the English literature from the initial citation of beta-blocker use in patients with asthma in 1976 through 2011 via PubMed, EMBASE, and SCOPUS using the following search terms: “cardioselective beta-blocker treatment of hypertension” AND “asthma”; “cardioselective beta-blockers” AND “asthma.” When pertinent articles were found, we assessed relevant articles cited in those papers. All studies and case reports related to the subject of cardioselective beta-blocker treatment of hypertension in patients with asthma were included. We did not include chronic obstructive pulmonary disease in our literature search, but specifically focused on asthma.

BETA-BLOCKER-INDUCED ASTHMA

Noncardioselective beta-blockers are well documented to induce bronchospasm in patients with asthma, and this subject has been extensively reviewed (3–6). In some patients, noncardioselective agents may cause severe bronchospasm and death (9–12). It is important to emphasize that even nonsystemic usage, such as with *ophthalmic* timolol has caused several cases of fatal asthma (13, 14).

Both dose and formulation can impact bronchospastic response. Cardioselective agents such as extended-release metoprolol (e.g., Toprol XL) are appropriate to use in patients with nonsevere asthma who have heart failure or

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a history of MI. Although extended-release metoprolol at doses not exceeding 100 mg daily may usually be well tolerated, the same margin of safety may not be true with immediate-release metoprolol. In a double-blind, randomized, crossover study of immediate-release metoprolol in 15 patients with asthma, 6 patients were withdrawn prematurely because of symptoms or decrease in forced expiratory volume in the first second (FEV₁) of >20% following an average tolerated cumulative dose of only 26.8 mg (15). Since there are multiple alternative classes of antihypertensive drugs available, these data are evidence of the risks inherent in therapeutic choices. Even with cardioselective beta-blockers, such as atenolol or extended-release metoprolol, caution should be used as doses are increased. With higher doses, cardioselectivity is reduced, and the risk of bronchospasm increases (6).

STUDIES OF CARDIOSELECTIVE BETA-BLOCKER TREATMENT OF HYPERTENSION IN PATIENTS WITH ASTHMA

In 1976, Formgren (16) reported the effect of metoprolol in the treatment of hypertension in 17 (12 males) patients with asthma. Metoprolol 50 mg twice daily and 100 mg twice daily given for 17 days were compared to a beta-blocker no longer in use (practolol) in a double-blind, randomized trial. All patients received oral terbutaline 25–5 mg 2–4 times daily along with inhaled terbutaline or albuterol 2–4 times daily during the study. In 13 patients, asthma treatment included long-term oral corticosteroids prior to the study. At the lower dose of 50 mg twice daily, metoprolol was well tolerated (symptoms and FEV₁). With the 100 mg twice daily dose, FEV₁ was reduced ($p < .01$), and 4 of 12 patients reported exacerbations of asthma.

Lawrence et al. (17) compared metoprolol 100 mg twice daily, atenolol 100 mg daily, and placebo each given for 3 weeks in a randomized, crossover study in 14 hypertensive patients (12 males) with asthma. The following asthma assessments were made over the 21-day period: number of asthma “attacks”, days without symptoms, inhalations of bronchodilator, degree of symptoms (1–5 scale), and peak expiratory flow (PEF) (morning and evening). The frequency of asthma “attacks” was reported more often with metoprolol ($p < .05$). All acute events occurred in six patients receiving metoprolol versus three patients receiving atenolol. Exacerbation-free days were less with atenolol ($p < .05$), but there was no significant difference in use of inhaled bronchodilators. The number of days of wheezing (moderate, severe, or very severe) was less with atenolol (50% vs. 74%, $p < .05$). PEF was reduced more with metoprolol than atenolol ($p < .05$) but only in the afternoon.

Jackson and Beevers (18) compared the effect of single doses of atenolol (100 mg) to the noncardioselective labetalol (300 mg) in 11 patients (six males) with asthma and hypertension. In this double-blind, placebo-controlled, crossover study, the FEV₁ was determined prior to the

administration of beta-blocker or placebo and again 2 hours later. Nebulized albuterol was then given, followed by repeat FEV₁. The median decrease in FEV₁ 2 hours post-treatment was 5% for placebo, 12% for atenolol, and 17% for labetalol, and median increase after albuterol treatment was 13% for placebo, 5% for atenolol, and 2% for labetalol.

Krauss et al. (19) evaluated the effect of atenolol in 12 patients (eight males) with hypertension and mild asthma over a period of up to 8 months. Fourteen patients enrolled in this open-label study, but one patient dropped out because her asthma worsened when her dose of atenolol reached 125 mg; another patient was dropped due to non-compliance. Patients received atenolol 50–100 mg daily, monitored PEF, and maintained a symptom diary. Atenolol therapy was well tolerated compared to baseline, with no increase in the number of episodes of dyspnea, no limitation in daily activity, no greater frequency in the use of albuterol, and a prompt response to albuterol. PEF values did not change compared to baseline (pre-atenolol).

In a single-dose, randomized, crossover study, Chatterjee (20) compared the effect of bisoprolol 10 and 20 mg with atenolol 100 mg and placebo in 12 patients (11 males) with asthma and hypertension. FEV₁ and PEF were measured before both cardioselective beta-blockers or placebo treatment and then at 30, 60, and 120 minutes post-dose. Albuterol was inhaled 5 minutes after the 2-hour measurement of FEV₁ and PEF, with subsequent determinations at 5, 15, 60, and 120 minutes. Compared to baseline, there were no significant differences with either of these two tests in any of the four treatment arms. The results following the albuterol dose at 5 and 120 minutes revealed significant increases in FEV₁ and PEF in all four treatment arms compared to baseline. However, there were no differences between the groups. No patients were discontinued from the study due to symptoms or had clinically relevant reduction in pulmonary function.

In 10 patients (three males) with asthma and mild to moderate hypertension, Van Zyl et al. (21) compared the effects of celiprolol and atenolol. Celiprolol is a cardioselective beta-blocker with intrinsic sympathomimetic activity. This double-blind, crossover study included a treatment period of 4 weeks with atenolol 100 mg daily and celiprolol 400 mg daily. Twelve patients were enrolled in the study, but one patient was withdrawn after severe bronchospasm associated with an upper respiratory infection during the placebo run-in phase. A second patient withdrew due to severe hypertension. Over the 4-week study period, patients kept symptom diaries, tracked inhaled bronchodilator requirements, and measured PEF twice daily. There were no differences reported in these measures with either of the two beta-blockers. Acute single-dose challenge with atenolol caused a drop in FEV₁ and PEF at 3 hours ($p < .01$), but improvement was noted after inhaled albuterol treatment ($p < .05$). No reduction in FEV₁ or PEF was seen with celiprolol after single-dose challenge.

Fogari et al. (22) compared the effect of celiprolol (200 mg daily), propranolol (80 mg daily), oxprenolol

TABLE 1.—Studies evaluating cardioselective beta-blocker treatment of hypertension in asthmatic patients.

Study	Number of patients	Beta-blocker (dosage/day)	Duration	Effect on asthma	Comments
Formgren (1976)	17	Metoprolol tartrate (100 and 200 mg) and practolol (200 and 400 mg)	17 days	Four out of 12 patients had asthma exacerbations when given beta-blocker at the higher dosage. All patients had significantly greater decline in FEV ₁ ($p < .01$) on beta-blockers compared to placebo period	Practolol, a beta-blocker no longer in use, is considered as relatively cardioselective
Lawrence (1982)	14	Metoprolol tartrate (200 mg), atenolol (100 mg), and placebo	21 days	Nine patients reported asthma exacerbations (six patients on metoprolol vs. three patients on atenolol). Fewer exacerbations ($p < .05$), more asthma-free days, and less effect on evening PEF seen with atenolol compared to metoprolol	
Jackson and Beevers (1983)	11	Atenolol (100 mg) and labetalol (300 mg)	3 days	Median decrease in FEV ₁ 2 hours after beta-blocker treatment was 5% for placebo, 12% for atenolol, and 17% for labetalol. After bronchodilator treatment, increase in FEV ₁ was 13% for placebo, 5% for atenolol, and 2% labetalol	
Krauss (1984)	14	Atenolol (50–125 mg)	8 months	Atenolol (50–100 mg/day) well tolerated by patients with no significant difference in episodes of dyspnea, frequency of bronchodilator usage, response to bronchodilator therapy, or limitation in daily activity	One patient dropped out of the study due to worsening of asthma when atenolol dosage reached 125 mg/day
Chatterjee (1986)	12	Bisoprolol (10 and 20 mg), atenolol (100 mg)	1 month	No significant differences observed between FEV ₁ and PEF before and after treatment with beta-blocker	
van Zyl (1989)	10	Atenolol (100 mg) or celiprolol (400 mg)	4 weeks	Acute single-dose challenge with atenolol, not celiprolol, resulted in significant drop in FEV ₁ and PEF at 3 hours ($p < .01$) but significant improvement after bronchodilator treatment ($p < .05$). No difference in long-term asthma control on beta-blocker therapy compared to placebo	Celiprolol is a cardioselective beta-blocker with intrinsic sympathomimetic activity
Fogari (1990)	10	Propranolol (80 mg), oxprenolol (80 mg), atenolol (100 mg), and celiprolol (200 mg)	7 days	FEV ₁ significantly reduced ($p < .05$ for both) and response to albuterol blocked with propranolol and oxprenolol. Effects not seen with cardioselective agents, atenolol, and celiprolol	Oxprenolol is a noncardioselective beta-blocker

Note: FEV₁, forced expiratory volume in the first second; PEF, peak expiratory flow.

(80 mg daily), and atenolol (100 mg daily) in 10 males with hypertension and asthma. In this randomized, crossover design study, patients received each treatment for 7 days. At the end of each week of treatment, FEV₁ was measured before and after albuterol inhalation. For the two noncardioselective agents (propranolol and oxprenolol), the FEV₁ was significantly reduced and the response to albuterol was inhibited. There were no statistically significant reductions from baseline in FEV₁ with atenolol or celiprolol. Response to inhaled albuterol was significant for both atenolol and celiprolol, but there was no difference between them. Table 1 summarizes the seven studies of cardioselective beta-blocker use in patients with asthma and hypertension.

SITUATIONS WHERE CARDIOSELECTIVE BETA-BLOCKERS HAVE INCREASED BENEFITS VERSUS RISKS IN PATIENTS WITH HYPERTENSION AND ASTHMA

As previously mentioned, there are two *compelling* indications for the use of cardioselective beta-blockers in patients

with asthma and hypertension. In patients with a history of MI or heart failure, beta-blockers decrease mortality and morbidity and consequently are established therapy based on extensive evidence (23, 24).

In addition, there are a number of situations where low to moderate doses of cardioselective beta-blockers *may* have benefits that outweigh risks in patients with concurrent nonsevere asthma and hypertension (Table 2). In these

TABLE 2.—Potential indications for cardioselective beta-blocker treatment of hypertension in patients with nonsevere asthma.

Adverse effects with other antihypertensive agents
Concomitant severe angina in patients when angioplasty or surgery is not a good option. Although nitrates and calcium-channel blockers are an option, cardioselective beta-blockers may also add benefit (25)
Patients with thyrotoxicosis (26)
Reduce perioperative complications? (see updated guidelines for specific indications) (27)
Hydralazine or minoxidil therapy required (beta-blockers are agents of choice to blunt reflex tachycardia) (28)

Notes: Controlled studies are needed to verify benefits outweigh risks. As discussed in the text, concomitant heart failure or history of MI is a compelling indication for cardioselective beta-blockers.

patients, continual monitoring for change in risk/benefit is obviously prudent. Studies are needed in these populations to verify that benefits outweigh risks.

DISCUSSION

When using cardioselective beta-blockers for the treatment of hypertension in patients with asthma, numerous factors impacting risk–benefit need to be considered. These have been recently described and include asthma severity classification and therapeutic plans for optimal long-term asthma management (29). For example, patients should have excellent control of asthma prior to initiating cardioselective beta-blocker therapy. Monitoring of the patient in the physician's office before and after the first dose of cardioselective beta-blocker should be done, including an FEV₁ or PEF and symptoms. If there are marked symptoms or the FEV₁ decreases of >20%, cardioselective beta-blocker therapy should not be continued. In patients with persistent asthma who tolerate the first beta-blocker dose, inhaled corticosteroids and other appropriate long-term therapy should be ongoing as well as excellent environmental control and optimal management of comorbidities such as allergic rhinitis (2). Similar to patients who are just starting appropriate long-term asthma management, spirometry should be monitored at 1–6-month intervals initially to ensure excellent asthma control is continued, and then at least at 1–2-year intervals (2). Throughout the duration of treatment with a cardioselective beta-blocker in selected patients with hypertension and well-controlled asthma, additional monitoring and attention to the asthma action plan (preferably PEF based as well as symptom based) are required.

Upon initiation of the written action plan for management of mild to moderate symptoms, if the patient experiences prompt response to an inhaled beta₂ agonist and/or inhaled ipratropium, then cardioselective beta-blocker therapy may be continued. Dose reduction of the beta-blocker may also be prudent; for example, in the patient who is receiving atenolol 100 mg daily, a decrease in dose to 50 mg daily would be appropriate (a similar dose reduction for metoprolol succinate would be warranted). If there is a repeated exacerbation for no obvious reason (i.e., a common identifiable asthma trigger), despite otherwise optimal asthma management per NIH Expert Panel Report 3 Guidelines, cardioselective beta-blocker therapy should be discontinued (2).

Although a recent hypothesis suggests chronic dosing of beta-blockers may be beneficial in asthma, extensive clinical research is required to determine whether this paradox has merit (30). Randomized controlled trials are needed to provide evidence of this possible effect.

As mentioned previously, if a clinician prescribes cardioselective beta-blocker therapy in a patient with asthma, a very careful assessment of asthma severity and control is absolutely essential. Early reports summarized in our review do not indicate whether asthma was well controlled prior to initiation of beta-blocker treatment. At the time these reports were published, extensive evidence supporting the value of

inhaled corticosteroids in improving outcomes was not available. Epstein (31) points out that cardioselective beta-blockers should be initiated at low doses and titrated upward as required. Both Epstein (31) and Salpeter et al. (4) support the conclusion that long-term safety (especially during acute asthma exacerbations) of cardioselective beta-blockers needs to be established. Frishman and Saunders (32) recently reviewed the use of beta-blockers in the treatment of hypertension and concluded that most beta-blockers should not be prescribed in patients with asthma (at least in the usual dose range for treating hypertension). Another concern is that asthma continues to be undiagnosed and undertreated (33). Thus, some patients may have beta-blocker therapy initiated for hypertension without the physician being aware that the patient has asthma.

The studies summarized in this review have very small patient populations and most are short term in duration. Especially considering the likely frequency of the comorbidities of asthma and hypertension, larger, randomized trials with longer follow-up periods are needed to determine how cardioselective beta-blockers are tolerated, including during asthma exacerbations, in hypertensive patients. Although a lack of support for large, randomized trials with an older class of drugs makes a definitive answer to this question unlikely, further observational studies that have larger patient populations could be of benefit.

DECLARATION OF INTEREST

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