Clinical Considerations Regarding β-Blocker Use in Patients with Reactive Airway Disease: A Report of 3 Cases

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A variety of diseases are commonly treated with β-blockers, including angina pectoris, coronary artery disease (CAD), hypertension, heart failure, cardiac arrhythmias, tremors, and thyrotoxicosis. American College of Cardiology/American Heart Association guidelines outline the use of metoprolol succinate, bisoprolol, or carvedilol as a class I recommendation in patients with chronic heart failure and recommend the use of perioperative β-blockers in patients undergoing vascular surgery (class I recommendation) and in patients with coronary heart disease undergoing intermediate-risk noncardiac surgery (class IIa recommendation).[1,2] Recent literature supports these recommendations in selected patients undergoing noncardiac surgery.[3,4] β-Blockers are efficacious and inexpensive and have been widely accepted as the standard of care for patients with the aforementioned conditions.[3,5]

β-Blockers work by binding to β_1-adrenoreceptors in the heart and subsequently blocking the action of endogenous catecholamines; however, β_2-adrenoreceptors in the airways can also be affected, resulting in bronchospasm.[6,7] Many patients treated with β-blockers have concomitant reactive airway disease (RAD), including asthma or chronic obstructive pulmonary disease (COPD) with a reversible obstructive component.[8] Up to 20% of patients with COPD also have CAD,[9] and the prevalence of COPD in patients with chronic heart failure has been reported at up to 32%.[10] Because β-blockers can worsen RAD, treating patients with these comorbid conditions poses a challenge to clinicians.

For many years, the use of β-blockers in patients with RAD was considered a contraindication because of the potential for bronchospasm. However, recent data appear to demonstrate the safety and efficacy of cardioselective β-blockers in patients with concomitant mild to moderate RAD, with some studies demonstrating a potential mortality benefit.[5,9,11] In light of these recent data favoring increased use of β-blockers, clinicians must be aware of their associated benefits and risks, especially in patients with moderate to severe RAD. This article presents 3 cases that highlight some common practices and potential limitations in prescribing β-blockers in patients with RAD and emphasizes the importance of using caution and monitoring these patients closely to improve patient safety and clinical outcomes.

CASE EXAMPLES

Case 1

A 50-year-old man with a history of hypertension and severe oxygen-dependent bullous emphysema with a forced expiratory volume in 1 second (FEV_1) of 0.85 L (27% predicted) was hospitalized for a COPD exacerbation. Six weeks prior to admission, he was started on metoprolol tartrate 50 mg twice daily. In the hospital, the patient became ventilator-dependent and failed multiple weaning trials. He subsequently underwent a tracheostomy and was transferred to a long-term care facility for further attempts at ventilator weaning. Six weeks after transfer, the pulmonary service was consulted because of the inability to wean the patient from the ventilator and persistent wheezing that was resistant to steroids and bronchodilators. The patient's medications included metoprolol tartrate 50 mg twice daily, inhaled budesonide, prednisone 10 mg twice daily, and a combination of nebulized ipratropium and albuterol. Metoprolol tartrate was tapered and discontinued. Five days later, the patient was successfully weaned from the ventilator and discharged home on 2 L of oxygen via nasal cannula.

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Case 2

A 68-year-old man with a past medical history of COPD, CAD, tobacco abuse, and peripheral vascular disease presented to his primary care physician with dyspnea on exertion. Two years prior to presentation, the patient's FEV_1 was 1.72 L (58% predicted), which was consistent with moderate COPD. The patient had a long history of stable dyspnea on exertion while taking a maintenance dose of metoprolol tartrate 50 mg twice daily. However, he began to experience shortness of breath at rest shortly after his cardiologist increased metoprolol tartrate from 50 mg twice daily to 100 mg twice daily to optimize treatment of his CAD. At the visit with his primary care physician, pulmonary function tests performed because of worsening symptoms showed that his FEV_1 had decreased to 1.01 L (37% predicted). Unaware that metoprolol was increased, the primary care physician referred the patient to a pulmonary specialist for evaluation of poorly controlled COPD. During the pulmonary visit, the correlation was made between the patient's shortness of breath at rest and the up-titration of the β-blocker. Metoprolol was subsequently discontinued, and the patient's shortness of breath at rest resolved. Four weeks later, repeat spirometry showed improvement in his FEV_1 to 1.3 L (48% predicted).

Case 3

An 82-year-old man with a history of systolic heart failure, CAD, chronic atrial fibrillation, asthma, and moderate COPD with an FEV_1 of 1.49 L (58% predicted) presented to the emergency department with a 6-week history of progressive shortness of breath associated with chest discomfort. Six weeks prior to presentation, he had experienced an abrupt decline in exercise tolerance that started shortly after metoprolol tartrate 12.5 mg twice daily was initiated for rate control of atrial fibrillation. The patient was admitted to the hospital, at which time the metoprolol tartrate was stopped and the patient's shortness of breath subsequently resolved. Low-dose sotalol (80 mg daily) was started, but the patient began to experience wheezing and dyspnea. Sotalol was consequently discontinued and the patient returned to baseline.

DISCUSSION

It is well-documented that β-blockers can be used in patients with stable mild to moderate RAD;[10,12–14] however, these medications have the potential to cause adverse outcomes in selected patients unless used with caution and close follow-up, as demonstrated by these 3 case presentations. In the first case patient, a β-blocker was started for hypertension. Although metoprolol tartrate is frequently used in the treatment of hypertension, it is contraindicated in patients with severe COPD, such as in the case patient. After careful review of the patient's medications, the consulting pulmonologist noted that the patient's acute respiratory decline and wheezing correlated with the initiation of metoprolol. Once the β-blocker was discontinued, the patient could be weaned from the ventilator and subsequently maintained on oxygen. Thus, when prescribing β-blockers, it is important to assess lung disease severity in patients with COPD. The second case illustrates the importance of selecting the appropriate doses of β-blockers in the presence of RAD as well as the need for physician-to-physician communication when adjusting medication and the importance of close follow-up with serial spirometry in patients with RAD. The case 2 patient had stable moderate RAD and was treated with low-dose metoprolol tartrate for CAD. When the β-blocker was increased to maximize treatment of his CAD, the patient's lung function deteriorated significantly. Selected patients with moderate RAD may tolerate moderate doses of cardioselective β-blockers, but shortness of breath may worsen with higher doses. Case presentation 3 demonstrates the importance of choosing β-blockers with appropriate cardioselectivity (ie, sotalol is a nonselective β-blocker with a high affinity for β_2-receptors) and illustrates that even low doses of cardioselective β-blockers can exacerbate moderate RAD. In summary, key points to consider when initiating β-blockers in patients with moderate to severe RAD include:

- Use cardioselective β-blockers if clinically indicated
- Increase β-blocker dose gradually and only if well-tolerated at lower doses
- Cardioselective β-blockers, even in low doses, may be harmful in selected patients
- Assess severity of lung disease at each visit
- Observe patients closely with serial spirometry
- Educate patients about medication changes and possible side effects

β-BLOCKERS AND REACTIVE AIRWAY DISEASE

The benefits of β-blockers in the treatment of heart failure and hypertension, after myocardial infarction (MI), and perioperatively in noncardiac surgeries have been clearly established. However, it is important to recognize that many studies demonstrating the benefits of β-blockers have excluded patients with COPD or asthma.[11] A recent meta-analysis by Salpeter and colleagues[5] that evaluated 381 adults with asthma from

29 studies concluded that the use of a single dose of a cardioselective β-blocker in patients with mild to moderate RAD resulted in only a small decrease (7.46%) in FEV_1 and was associated with an increased FEV_1 response to β-agonists as compared with placebo. Continued administration of β-blockers (range, 3 days–4 wk) resulted in no significant change in FEV_1, respiratory symptoms, or inhaler use compared with placebo in patients with mild to moderate RAD. However, very few patients with severe RAD were included in the selected studies, and patients with recent asthma exacerbations were often excluded. Furthermore, several studies included in the meta-analysis were limited to the use of single-dose β-blockers or β-blockers given over a brief period.[5] In a review of 20 studies evaluating the effects of cardioselective β-blockers in patients with COPD, Salpeter and colleagues[12] found no change in respiratory symptoms or FEV_1 compared with placebo (treatment duration, 2 days–12 wk). In addition, treatment response to β_2-agonists as judged by improvement in FEV_1 was not affected.[12] More studies are needed to further investigate the effects of β-blocker therapy in patients with moderate to severe COPD as well as in patients on long-term therapy.

Gottlieb and colleagues[11] suggest that using β-blockers after MI in patients with conditions that are often considered contraindications to β-blockade has a beneficial effect on mortality, even in patients with COPD. Similarly, a recent retrospective study demonstrated that β-blocker use among patients with COPD exacerbations was well tolerated and may be associated with reduced mortality.[9] However, the β-blocker doses used in trials establishing their value after acute MI are relatively high (metoprolol succinate 200 mg daily and carvedilol 25 mg twice daily), and many physicians attempt to titrate these medications to optimize their cardiac benefit. It is well accepted that high-dose β-blockers are more likely to cause bronchospasm and reduce pulmonary function in patients with moderate to severe RAD.[13] Additionally, there is no evidence in the literature to suggest that the use of low-dose β-blockers will prolong life after MI. Further studies are warranted to determine whether the benefits of starting low-dose β-blockers in patients with severe RAD and concomitant CAD outweigh the risks from a respiratory standpoint.

Considering Cardioselectivity

Many physicians share the perception that there is no need to closely monitor patients with mild to moderate RAD after initiating low-dose cardioselective β-blockers since their safety in this patient population has been considered acceptable.[5] However, disease severity can change quickly over time and pulmonary symptoms can worsen, thus necessitating close follow-up. With regards to cardioselectivity, it is important to recognize that no agent is absolutely β_1-adrenoreceptor–specific, and that the β_1/β_2 selectivity of most β-blockers used in clinical practice is poor in intact living cells.[13] Some compounds that have traditionally been considered β_1-selective may actually have variable affinity for the β_2-adrenoreceptor. For example, low-dose atenolol has greater β_1 selectivity than metoprolol and appears to be one of the safest β_1-blockers for use in patients with asthma.[6] The **Table** lists some selective and nonselective β-blockers and their relative selectivity for β_1- versus β_2-receptors.[6]

Table. Selectivity Ratios for Selective and Nonselective β-Blockers*

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Adapted by permission from Macmillan Publishers Ltd. Baker JG. The selectivity of β-adrenoreceptor antagonists at the human β1, β2 and β3 adrenoreceptors. Br J Pharmacol 2005;144:321.

*A ratio of 1 demonstrates no selectivity for a given receptor subtype over another.

It is difficult to predict which patients with RAD will have an adverse effect from β-blocker therapy. Both cardioselective and nonselective β-blockers have been associated with increased hospitalizations and emergency department visits due to asthma/COPD in asthmatic patients with or without COPD as compared with controls.[15] In patients with COPD, cardioselective β-blockers increased the risk of emergency department visits but reduced the risk of hospitalizations.[15] Some have even suggested that physicians should consider obtaining informed consent from patients with mild to moderate RAD prior to initiating β-blocker therapy.[14]

CONCLUSION

These 3 cases exemplify the potential risks associated with the use of selective β-blockers, even in low doses, in selected patients with moderate to severe RAD. Furthermore, these cases were not rare events and were seen over a 6-month period; several more cases have been identified in the past year. It appears that aggressive use of β-blockers may be increasing,

even in patients with severe RAD. This increased use may lead to greater potential benefits as well as increased adverse outcomes in selected patients. Further research is needed to determine the effect of long-term treatment with cardioselective β-blockers in patients with moderate to severe RAD, to examine β-blocker use during hospital admissions for acute exacerbations in which airway function is most severely compromised, to identify the threshold dose that would be cardioprotective in patients with an acute MI and concomitant RAD, and to develop more selective β-blockers. In the meantime, it is important to individualize medical treatment for each patient and monitor patients closely for medication side effects. **HP**

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