β-blockers in airway disease

Learning objectives
After completing this activity, pharmacists should be able to:

- Identify benefits of β-blockers in cardiovascular disease
- Be aware of the potential benefits of β-blockers in airway disease
- Counsel patients on benefits and risks of β-blockers in airway disease.

This activity has been accredited by the Pharmaceutical Society of Australia as a Group 2 activity for 1 point. Accreditation number: CX090048i.

PSA is authorised by the Australian Pharmacy Council to accredit providers of CPD activities for pharmacists that may be used as supporting evidence of continuing competence.

The competency standards addressed by this activity include (but may not be limited to) 3.1.1, 3.1.2, 3.1.3, 3.2.2, 6.1.1, 6.1.2, 6.1.3, 6.2.2, 6.3.2.

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Multimorbidity
Many people, particularly as they grow older, have several chronic medical conditions, which is referred to as multimorbidity. The commonly used term comorbidity implies an index disease to which coexistent diseases relate and may share aetiology and perhaps a solution. Multimorbidity is defined as the co-occurrence of 2 or more diseases in one person without defining the index-disease.

In clinical practice, people often have multiple conditions which require greatly differing and often incompatible management. Multimorbidity can influence treatment decisions and therefore treatment outcomes. The problems then encountered include conflicting treatment recommendations in guidelines for optimal management of each condition and complex treatment regimens that patients are expected to follow.

A medication with proven benefit in one condition, may potentially cause harm in a patient with other conditions. One such as example is the use of β-blockers in patients with airway disease.

β-blockers and heart failure
A paradigm shift has been evidenced since the late 1980s with the use of β-blockers in heart failure. A decade ago, β-blockers were contraindicated in heart failure. Now guidelines suggest the routine use of β-blockers.¹

Beta-blockers are recommended, unless not tolerated or contraindicated, for all patients with systolic heart failure who remain mildly to moderately symptomatic despite appropriate doses of an ACE inhibitor. Beta-blockers are also indicated for patients with symptoms of advanced heart failure.²
Acute doses can produce deterioration in myocardial contractility with increased cardiac index and stroke volume and can tip a patient into an acute decompensated state. Hence, β-blockers should not be initiated during a phase of acute decompensation, but only after the patient’s condition has stabilized. Beginning at low doses with gradual increases limits adverse effects such as hypotension and bradycardia.

Chronic dosing with β-blockers produces beneficial effects and reduces deaths in heart failure.³

β-blockers and airway disease
Many patients with asthma or chronic obstructive pulmonary disease (COPD) will have coexisting cardiovascular disease. Mortality benefit of beta-blockers in patients with hypertension, heart failure and coronary artery disease is well established.⁴

However many patients with the multiple morbidities of cardiovascular disease and asthma or COPD are not prescribed β-blockers. For example, patients with acute coronary syndrome and a history of reversible airways disease are more than 40% more likely to have β-blockers omitted in first 24 hours of admission and 55% more likely not to receive a β-blocker at discharge.⁵ The benefits of β-blockers in reducing re-infarctions and mortality after an acute myocardial infarction may outweigh the risks in patients with asthma or COPD.⁶

In a landmark retrospective study of 46,000 patients, Gottlieb et al demonstrated a 40% risk reduction for mortality in those patients discharged from the hospital with a β-blocker prescription. The overall β-blocker prescription rate during the study period was 34% in all patients and 18% in those with an asthma diagnosis. Interestingly, the subset with asthma also enjoyed a risk reduction of 40% for mortality. They had a higher mortality rate but same percentage risk reduction.⁴ In a later publication analyzing a subset of patients with severe asthma, the mortality benefit of β-blockers for coronary artery disease was not found.

Many references still list the use of β-blockers as a contraindication in patients with asthma or COPD.

Reversible airways disease – contraindicated. (AMH 2009)

Asthma remains a contraindication to the use of any of the beta blockers. Non-selective beta blockers should be strictly avoided in patients with asthma. (eTG)

The original evidence of a potential adverse effect of beta-blockers in reversible airway disease was based on case reports of acute bronchospasm precipitated by high doses of non-cardioselective blockers, presumably due to their blockade of β₂ receptors on bronchial smooth muscle.

Emerging evidence now suggests that while single doses of cardioselective beta-blockers can reduce respiratory function, chronic dosing does not cause such an effect nor impair the acute response to a beta-agonist such as salbutamol.⁷

This paradoxical pharmacology may be partially explained by the upregulation of β₂ adrenoreceptors that occurs with chronic dosing of β-blockers.⁸ Downregulation and worsening of asthma control can occur with chronic exposure to β₂ agonists.

Cardioselective β-blockers
Cardioselective beta-blockers, or β₁-blockers, have over 20 times more affinity for β₁ receptors as for β₂ receptors, and theoretically should have significantly less risk for bronchoconstriction.
β₁ receptors are primarily found in the heart, and β₂ receptors in airway smooth muscle. Ninety percent of β-receptors in the lung located on alveoli and are mainly β₂; 10% are found on airways and are mainly β₁.

Cardioselective β-blockers available in Australia include atenolol, metoprolol and bisoprolol.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>ISA</th>
<th>Lipid solubility</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>-</td>
<td>-</td>
<td>Renal</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>-</td>
<td>-</td>
<td>Hepatic/renal</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>α1, β1, β2</td>
<td>-</td>
<td>++</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Labetalol</td>
<td>α1, β1, β2</td>
<td>-</td>
<td>+</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>-</td>
<td>+</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>β1, β2</td>
<td>+</td>
<td>+</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Pindolol</td>
<td>β1, β2</td>
<td>++</td>
<td>+</td>
<td>Hepatic/renal</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β1, β2</td>
<td>-</td>
<td>++</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

**Asthma and COPD**

In the past, asthma and COPD were thought to represent clearly distinguishable diseases: asthma was seen as a treatment-responsive and reversible inflammatory process, while COPD has been characterised by fixed and progressive airway narrowing and alveolar destruction not responsive to treatment. Current definitions emphasise these features as the classical form of each disease, but acknowledge that there can be significant overlap between asthma and COPD.

**β-blockers and asthma**

Asthma is a chronic inflammatory disorder of the airways with recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Patients have variable symptoms and spirometry shows significantly reversible airflow limitation.

A Cochrane review pooled the data up to 2007 from 29 randomized placebo-controlled trials on the use of cardioselective beta-blockers in patients with reversible airway disease. The results showed that, compared to placebo, the first dose of active treatment produced a small drop in FEV₁ which was not associated with adverse respiratory effects. After continued treatment for a few days to weeks there was no difference in FEV₁, symptoms or incidence of inhaler use. The cardioselective blockers that were included in the study and available in Australia were atenolol, metoprolol, and bisoprolol.

It has been suggested that use of a selective anticholinergic such as tiotropium could prevent β-blocker induced bronchoconstriction with initial doses.

This meta-analysis had several limitations:
- most of the participants were relatively young with mild to moderate airway obstruction
- those with recent asthma exacerbation were often excluded from study
- many of the studies were of short duration (3 days to 4 weeks)

Conclusions from the meta-analysis were that cardioselective β-blockers do not produce clinical significant adverse respiratory effects in patients with mild to moderate reversible airway disease (asthma).
Patients with severe persistent asthma with daily daytime symptoms, frequent night-time symptoms and frequent exacerbations should avoid β-blocker medications.

<table>
<thead>
<tr>
<th></th>
<th>Daytime asthma symptoms</th>
<th>Night-time asthma symptoms</th>
<th>Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermittent</strong></td>
<td>&lt; weekly</td>
<td>&lt; 2 per month</td>
<td>Infrequent, brief</td>
</tr>
<tr>
<td><strong>Mild persistent</strong></td>
<td>weekly &amp; &lt; daily</td>
<td>&gt; 2 per month but not weekly</td>
<td>Occasional, may affect activity or sleep</td>
</tr>
<tr>
<td><strong>Moderate persistent</strong></td>
<td>Daily</td>
<td>Weekly or more often</td>
<td>Occasional, may affect activity or sleep</td>
</tr>
<tr>
<td><strong>Severe persistent</strong></td>
<td>Daily – physical activity restricted</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

**β-blockers and COPD**
Chronic obstructive pulmonary disease (COPD) is a progressive, disabling disease characterised by symptoms of breathlessness during physical activity and/or daily cough with or without sputum, airway inflammation and airflow limitation that is not fully reversible.

Patients with COPD are at greater risk of ischaemic heart disease than those with asthma, so would benefit from the use of beta-blockers.

A meta-analysis of 11 single dose studies and 8 continued treatment studies showed that cardioselective β-blockers produced no significant change in FEV1 or respiratory symptoms compared to placebo in patients with COPD.10 A sub-group analysis showed no significant change in results for patients with severe COPD or for those with a reversible component.

The results from the 2007 Cochrane review were similar for patients with concomitant COPD.9 Another Cochrane review looking specifically at trials in COPD again demonstrated no adverse respiratory effects with cardioselective β-blockers.11 These medications did not affect the FEV1 treatment response to β2-agonists.

Non-selective β-blockers such as propranolol have been shown to worsen FEV1, airway hyperresponsiveness and impair bronchodilating effect of β2-agonists in patients with COPD.12

**Conclusions**
Given their demonstrated benefit in conditions such as heart failure, cardiac arrhythmias and hypertension, cardioselective β-blockers should not be routinely withheld from patients with mild to moderate asthma or COPD. Cardioselective beta-blockers do not produce significant reduction in airway function or increase the incidence of exacerbations in patients with COPD or mild to moderate asthma. The risks and benefits need to be assessed for individual patients.

*Declaration: This review was presented by Debbie Rigby at the AACP Forum at PAC 09 conference in October 2009.*
MCQs
1. Which of the following statements concerning the use of β-blockers and β-agonists in asthma is incorrect?
   a) Long-term use of β agonists is associated with increased morbidity and mortality
   b) Long-term use of all β-blockers may be beneficial
   c) Chronic use of cardioselective β-blockers may provide bronchoprotection
   d) Cardioselective β-blockers do not produce clinical significant adverse respiratory effects in patients with mild to moderate asthma

2. Which of the following β antagonists is not cardioselective?
   a) Carvedilol
   b) Atenolol
   c) Metoprolol
   d) Bisoprolol

3. Which of the following statements is incorrect?
   a) Cardioselective β-blockers do not worsen respiratory symptoms in patients with COPD
   b) Cardioselective β-blockers do not worsen respiratory symptoms in patients with mild to moderate asthma
   c) Non-selective β-blockers may worsen airway hyperresponsiveness in patients with COPD
   d) Non-selective β-blockers do not worsen respiratory symptoms in patients with mild to moderate asthma

4. Beta-blockers have proven benefit in which of the following conditions?
   a) Acute coronary syndrome
   b) Heart failure
   c) Post-acute myocardial infarction
   d) All of the above

5. Regarding the use of β-blockers in patients with asthma, which of the following actions is incorrect?
   a) β-blockers may produce bronchial hyperresponsiveness with chronic use
   b) β-blockers may provide bronchoprotection with chronic use
   c) β-blockers produce bronchoconstriction with acute use
   d) β-blockers can produce asthma worsening with acute use

Answer these self assessment questions on this CE activity on the [www.auspharm.net.au](http://www.auspharm.net.au) website (immediate feedback provided)
References

1 National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006.
8 Lipworth BJ. β blockers for asthma: a double-edged sword. Lancet 2009;373:104-5.