Beta-blockers in asthma and chronic obstructive pulmonary disease

– shouldn't be used or underused?

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Introduction

The discovery of propranolol by Sir James Black in the 1960s has been described as one of the greatest breakthroughs in the treatment of cardiac disease since the discovery of digitalis.[1] He hypothesised that the use of beta-adrenoceptor antagonists (or beta-blockers) would reduce cardiac ischaemia by decreasing cardiac oxygen demand in patients with angina pectoris. Since then, beta-blockers have become fundamental to the treatment of a number of common cardiovascular conditions such as hypertension, angina pectoris, tachyarrhythmias, and heart failure, as well as reducing the risk of mortality and re-infarction following acute myocardial infarction.[2]

Given the overwhelming evidence for the benefit of beta-blockers in cardiac disease, they are still being underutilised in older patients, and in patients with airways disease, peripheral vascular disease and heart failure. Clinicians may be hesitant to prescribe beta-blockers in these conditions due to the perceived risk of adverse events, despite the fact that such patients are likely to benefit most.[3] Notably, patients with chronic obstructive pulmonary disease (COPD) have rates of co-existing cardiovascular disease that are higher than the general population, and mortality from ischaemic heart disease is greater than from the underlying airways disease.[4]

Why are beta-blockers underutilised?

There are a number of reasons why beta-blockers may be underutilised, the most commonly cited is the potential for adverse reactions, notably bronchospasm. However, many of the previously defined relative or absolute contraindications for beta-blockers have been questioned, including impaired LV function, diabetes and advanced age, and subsequently invalidated.

The original evidence suggesting caution in the use of beta-blockers in airways disease is based on experience with earlier generations of agents which were non-cardioselective. Studies on propanolol in the 1960s demonstrated acute reductions in forced expiratory volume in one second (FEV_1) in some asthmatic patients following drug administration, leading to the recommendation that propranolol should be contra-indicated in asthma.[5,6] Non-cardioselective drugs not only block beta-1 adrenoceptors, resulting in negative inotropic and chronotropic effects, but also block the beta-2 adrenoceptors in airway smooth muscle, with the potential for bronchoconstriction. This effect is less marked with so-called cardioselective beta-blockers such as atenolol and metoprolol, whose beta-1:beta-2 selectivity is at least 20:1. Thus, at therapeutic doses, the effect on beta-2 adrenoceptors is negligible.[7]

What evidence is there that beta-blockers cause adverse events in asthma or COPD?

Two Cochrane analyses, which address this question, have been reported. They focused on the use of cardioselective beta-blockers only.

The first meta-analysis investigated the use of cardioselective beta-blockers in patients with reversible airways disease.[8] This review analysed 29 randomised placebo-controlled trials, but made no distinction between asthma or COPD. However, the criteria for inclusion into the meta-analysis included that subjects had documented reversible airways disease, as demonstrated by an

increase of 15% in FEV_1 in response to beta-2 agonist.

Studies that investigated the use of either oral or intravenous beta-blocker were included, as were studies that investigated both the effects of a single dose or continuous treatment over a period of weeks. The outcome measures were: a change in FEV_1 in response to placebo or active drug, respiratory symptoms (wheeze, dyspnoea or an exacerbation of airway obstruction) and the requirement to use inhaled beta-2 agonist as a rescue medication.

In the analysis of the studies administering a single dose, there was a mean initial fall in FEV_1 of 7.5% (95% CI: 5.6–9.3%) compared to placebo, but there was also an increased response to beta-2 agonist implying that this effect is reversible. Overall, despite the fall in FEV_1, there was no difference in the frequency of adverse respiratory events.

In the analysis of studies investigating continuous treatment with beta-blockers, ranging from a few days to weeks, there was no difference in FEV_1, respiratory symptoms or reliever inhaler use compared to placebo.

The second meta-analysis focused specifically on patients with a diagnosis of COPD.[9] Data from 20 homogeneous, randomised, blinded controlled trials investigating the use of cardioselective beta-blockers in patients with COPD were pooled. There were no inclusions or exclusions based on the degree of reversibility of airway obstruction. Intervention included intravenous or oral beta-blocker versus placebo, as either a single dose or continuously over time.

The outcome measures were similar to the first analysis, namely a change in FEV_1 compared to baseline and compared to placebo, and reported symptoms such as wheezing, dyspnoea or an exacerbation. Results confirmed that cardioselective beta-blockers, given as a single dose or over longer intervals, produced no change in FEV_1 or respiratory symptoms compared to placebo. They did not affect response to beta-2 agonist. Importantly, these findings were similar in a sub-group of patients whose FEV_1 was less than 1.4 litres (or <50% predicted) and/or in those with more than 15% reversibility.

Table 1. Cardioselective vs non-cardioselective beta-blockers available in New Zealand

Cardioselective	Non-cardioselective
Acebutolol	Carvedolol, Sotalol
Atenolol	Labetolol, Timolol
Celiprolol	Nadolol
Esmolol	Pindolol
Metoprolol	Propanolol

Current evidence indicates that cardioselective beta-blockers are not contraindicated in patients with airways disease, and they may be especially useful in patients with COPD due to their increased risk of cardiovascular mortality… However, it is still appropriate to apply certain provisos

These meta-analyses have a number of limitations. Most of the studies included were small and the majority of participants were men. The participants were also relatively young, with the eldest patient being 65 years of age. It is uncertain whether the findings can be generalised to a more elderly population. Furthermore, the studies were generally short in duration, usually a matter of weeks rather than months – there appears to be no data on the long-term use of beta-blockers in these populations. Thus, although there were no differences in the rate of exacerbations compared to placebo, it remains possible that beta-blocker use in the long-term might result in more frequent or perhaps more severe exacerbations. Also, in the analysis in relation to reversibility, the severity of asthma was not clearly defined[10] and only patients with mild–moderate airway obstruction were investigated.

Finally, as with any meta-analysis, the conclusions drawn apply to a population and not an individual. Idiosyncratic responses are unpredictable. There are case reports of fatal adverse reactions to beta-blockers in individuals[11] but this is true with a number of other commonly used therapies. Although it is likely that such events will be few and far between, the *average* patient with asthma or COPD is unlikely to experience significant adverse respiratory effects with beta-blocker therapy.

Conclusion

Current evidence indicates that cardioselective beta-blockers are not contraindicated in patients with airways disease, and they may be especially useful in patients with COPD due to their increased risk of cardiovascular mortality. Overly cautious clinicians may be denying important benefits to a group of patients with significant co-morbidity.

However, it is still appropriate to apply certain provisos, which are themselves not evidence-based, to minimise the risk of adverse reactions. It is logical not to use beta-blockers in patients with severe asthma, particularly if it is unstable or the patient is prone to severe exacerbations. Moreover, during an exacerbation, beta-blockers should probably be temporarily withheld at a time when beta-blockade may be naturally increased due the effects of pro-inflammatory cytokines.[12] It would also be

prudent to offer a test dose and/or to titrate the dose of beta-blocker at the commencement of treatment to ensure tolerability. Finally, the key to successful treatment should also include patient education of the benefits and risks of beta-blocker use and also to maintain optimal control of their airway disease.

Key points from the meta-analyses:

- Beta-blockers reduce mortality in patients with cardiovascular disease, of which there is a high prevalence in patients with COPD.
- In reversible airways disease, a single dose reduces FEV_1 but response to beta-2 agonist is preserved. Continuous treatment with higher doses of cardioselective beta-blockers appears not to have a detrimental effect on FEV_1 or respiratory symptoms.
- In COPD, the use of cardioselective beta-blockers is unlikely to have a significant effect on FEV_1, respiratory symptoms or response to beta-2 agonists, even in severe airway obstruction.
- Treatment can be initiated at low doses and titrated upwards if there are no clinically adverse reactions.

Key recommendations

- Cardioselective beta-blockers may be used in patients with COPD or asthma that is mild-moderate and well-controlled.
- Patients should be optimally medicated with inhaled corticosteroids with or without long-acting beta agonist medication as appropriate, prior to starting beta-blockers.
- Beta-blockers should not be used in patients who have a history of brittle asthma or severe exacerbations.[10]
- There are no definitive data on the benefits of withholding beta-blockers during an exacerbation but it seems prudent to do so.[10]
- In high-risk individuals, after an initial test dose, the dose of beta-blockers should be titrated slowly upwards to ensure tolerability.
- Patients should be educated about potential side-effects, particularly during an exacerbation.

Competing interests

None declared.

References

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Suicide risk in adolescent depression

'Suicide is the most feared outcome of psychiatric illness. Among 10,000 children and adolescents who begin taking antidepressants for depression, approximately six will die by suicide during the next six months, and another 30 will be hospitalized after a serious suicide attempt. For adults, the corresponding numbers are four suicide deaths and 10 hospitalizations for suicide attempts. Of those 10,000 children and adolescents, approximately 3000 will stop taking their medication within a few weeks, 4000 will never return for a follow-up visit, and 6000 will not recover from depression during the next six months. Although the rates of antidepressant use have increased dramatically among both adults and adolescents during the past 20 years, the disappointing quality and outcomes of depression treatment have changed little. Our treatment of depression is growing wider, but it is often only inches deep.'

Simon G E. The Antidepressant Quandary - Considering Suicide Risk When Treating Adolescent Depression. N Eng J Med 2006; 355:2722-2723.