LETTERS

Is the coprescription of β blockers and β_2 agonists justified in COPD?

Dransfield and colleagues[1] advocate the use of β blockers even in patients admitted with acute exacerbations of chronic obstructive pulmonary disease (COPD), but certain points need further discussion.

Their retrospective analysis highlights the discordance in practice that exists between cardiologist and pulmonologist. Indeed, the former is keen to commence β blockers in patients with a wide range of cardiovascular diseases for cardioprotection, while the latter is cautious in protecting patients with obstructive airway disease from bronchoconstriction.

Historically, the use of β adrenergic blockers in patients with obstructive airways disease has been discouraged. There are currently no prospective long term data on the safety of β blockers in COPD and, moreover, β blockers are contraindicated in asthma. It is not always easy to differentiate between asthma and COPD, especially when inhaled therapy for both conditions is very similar.

Regarding the use of β blockers in patients with obstructive airways disease, the advice in the *British National Formulary*[2] reads as follows: β blockers may precipitate bronchospasm and this effect can be dangerous. β Blockers should be avoided in patients with a history of COPD or asthma, if there is no alternative, a cardioselective β blocker may be used with extreme caution under specialist supervision.

Even a prospective study[3] has suggested that non-selective β blockers are detrimental in patients with COPD. For instance, propranolol has been shown to worsen lung function and desensitise the airway to the bronchodilating effects of long acting β_2 agonists, while metoprolol, which has been advocated by the authors to be safe in COPD because of its cardioselectivity, significantly increased the extent of bronchial hyperresponsiveness. Until data from long term studies that specifically address these safety issues are available, the jury must still be out in deciding whether any β blockers are safe in COPD.

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Authors' response

We appreciate Dr Singh's interest in our paper and the thoughtful comments. While we believe our data make a compelling argument that β blockers are regularly tolerated by patients suffering acute exacerbations of COPD and that they may be associated with improved outcomes, we do not advocate their routine use at present and believe this overstates our conclusions.[1] We echo Dr Singh's call for randomised clinical trials in a variety of settings to definitively address the safety and efficacy of β blockers in patients with COPD.

Although observational studies, including ours[1–3], have suggested that β blockers are safe and effective in COPD patients with or at risk for cardiovascular disease, these results are not definitive and do not justify a change in clinical practice. Such studies cannot fully account for provider bias in the prescription of β blockers that is inevitable in retrospective analyses, and our results do not support the initiation of these drugs on admission to the hospital. In addition, Dr Singh correctly highlights that there are mechanistic studies that demonstrate adverse effects of β blockers on lung function,[4] although for cardioselective agents these effects appear modest.[5] Given the current evidence, we do recommend against the routine withholding of cardioselective β blockers from patients with COPD as this may be associated with increased mortality, particularly if the agents are acutely withdrawn.

Most guidelines list COPD as a contraindication to β blocker use although this is largely based on extrapolation of data in patients with asthma and from studies of non-cardioselective agents. Unlike mortality among patients with asthma, however, the most common cause of mortality in patients with COPD is cardiovascular disease. Thus the potential benefits of β blocker therapy are far clearer in this population. There are several mechanisms by which β blocker use during acute exacerbations may reduce mortality[1 6] and an important conclusion from our study is that β blockers are well tolerated even when the airway is most compromised. We believe that this finding, along with other observational studies suggesting benefit, sets the stage for randomised trials in outpatients with stable COPD to definitively establish the risk–benefit ratio of β blockers in COPD. If a benefit is observed, such a trial could change practice and we may finally have a drug to save lives in COPD.

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Biases in the observational study of β blockers in COPD

Dransfield and colleagues[1] reported, using an observational study design, that inpatient use of β blockers by patients hospitalised for COPD is associated with a surprisingly important 61% reduction in mortality.[1] They also reported an astonishing 92% reduction in mortality associated with short acting β agonist use. Several biases introduced in the design and analysis of this observational study must be considered when interpreting these startling mortality reductions in patients with COPD.

Firstly, immortal time bias was introduced by defining exposure to β blockers or to short acting β agonists by billings occurring at any time during the hospitalisation.[2] Indeed, the exposed patients necessarily had some initial period with no exposure before they received these drugs during the course of their hospitalisation. This period is "immortal": a patient whose hospitalisation lasted 8 days and who received a β blocker on day 5 had an immortal period of 5 days during which they could not die. Indeed, had the patient died on day 4, they would have been classified as a non-user of β blockers. Thus by defining exposure in this way, the immortal period conferred a guaranteed survival advantage to the users of β blockers and an apparently longer survival. This is suggested by the mean length of stay of 7.8 days for users of β blockers versus