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.

A Singh

Correspondence to: Dr A Singh, Department of Pulmonary Medicine, Christian Medical College and Hospital, Ludhiana 141010, India; drsinghakashdeep@gmail.com

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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.

M T Dransfield, S M Rowe, J Johnson, W Bailey, L Gerald

University of Alabama at Birmingham and the Birmingham VA Medical Center, Birmingham, Alabama, USA

Correspondence to: Dr M T Dransfield, University of Alabama at Birmingham and the Birmingham VA Medical Center, 215 THT 1900 University Blvd, Birmingham, AL 35294, USA; mdransfield99@msn.com

Competing interests: None.

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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

5.3 days for non-users. This bias unquestionably explains the phenomenal 92% reduction in mortality associated with short acting β agonists as over 95% of subjects used the agents and the magnitude of the bias is directly proportional to the frequency of exposure.[3]

Secondly, bias was introduced if β blockers are less likely to be used in the fatal hospitalisation of a patient with COPD who is in the final stages of the disease. Indeed, if these drugs are withheld in the context of palliative care, the rate of death in patients exposed to β blockers will be underestimated, which will make β blockers appear protective.

Thirdly, selection bias was likely introduced by the way the cohort was defined. The cohort of 825 subjects was formed using the last hospitalisation for a COPD exacerbation that occurred during the period 1999–2006. There were, however, approximately 2120 hospitalisations that occurred during this period (calculated from table 1 of the paper). By selecting the last hospitalisation, the cohort necessarily overrepresented the hospitalisations resulting in death. Basic tenets of epidemiology propose instead to use either the first hospitalisation to define the cohort, or to use all hospitalisations, albeit with a data analysis complicated by the correlated nature of hospitalisations occurring in an individual patient. Selection bias is amplified if β blockers are likely to be withheld in fatal hospitalisations.

Another important source of selection bias was introduced by identifying study subjects according to death summaries citing COPD as the probable cause of death. As death from cardiovascular causes is frequent in patients with COPD,[4] and as patients prescribed a β blocker, and therefore with cardiovascular disease, are less likely to have COPD listed as the cause of death,[5] subjects with COPD receiving a β blocker who died were systematically less likely to be included. As a result, a significant number of deaths exposed to β blockers was likely left out, leaving only eight such subjects in the study, thus leading to the appearance of a protective effect of β blockers. The presence of this bias is further suggested by the trend towards a protective effect of calcium channel blockers (odds ratio 0.76).

Observational studies are essential to complement information from randomised controlled trials. However, when such studies suggest astounding benefits that are inconsistent with trial data and use methods that are known to introduce well recognised biases, their results regrettably must be considered unfounded.

S Suissa, P Ernst

Center for Clinical Epidemiology and McGill Pharmacoepidemiology Research Unit, Jewish General Hospital, and Departments of Epidemiology and Biostatistics and of Medicine, McGill University, Montreal, QC Canada

Correspondence to: Dr S Suissa, Center for Clinical Epidemiology, Jewish General Hospital, 3755 Côte-Sainte-Catherine Road, Montréal, Québec, Canada H3T 1E2; samy.suissa@mcgill.ca

Competing interests: None declared.

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Authors' response

We thank Suissa and Ernst for their important comments regarding our paper and the design of observational studies. They raise several methodological concerns that call into question the validity of the results and highlight the many limitations of observational studies, including ours. It is certainly possible that immortal time bias and selection bias may have confounded our results and inflated the mortality benefit we observed with β blocker use; however, we strongly disagree that the results are inconsistent with clinical trial data as no randomised studies examining the effect of β blockers on COPD exacerbations or mortality exist. In fact, our results are entirely consistent with the few randomised studies of cardioselective β blocker use in COPD patients which suggest no harmful effects on lung function,[1] and with the majority of observational studies of β blocker use in patients with COPD which suggest benefit.[2–5]

Our study included a number of controls to appropriately account for confounding. Principally among them was the finding that in contrast with β blockers, calcium channel blockers were not associated with a beneficial effect on mortality, arguing against a healthy user bias. Drs Suissa and Ernst point out that there was a trend towards a protective benefit with calcium channel blockers but this was not significant and the effect size was far smaller than that observed with β blockers. We should point out that the pharmacy billing dataset did not include the date patients were charged for β blockers and thus we could not eliminate immortal time bias. However, because β blockers are much more likely to be instituted during the chronic care of the patient with COPD, rather than during the hospitalisation itself, this effect is likely reduced.

As suggested, we did examine the data using the first hospitalisation as the index event and found similar results to those we report. This approach supports the conclusions in the manuscript but does not allow for the inclusion of exacerbation frequency as a measure of disease severity which we viewed as critical to the analysis. Although our methodology for subject selection is not immune to bias, we did not select patients for inclusion based on a death summary citing COPD as the cause of death, as is suggested. We included all patients admitted with a primary diagnosis of COPD or a secondary diagnosis of COPD with a primary diagnosis of respiratory failure regardless of their hospital outcomes. Importantly, it is highly unlikely that β blocker use among patients with COPD with cardiovascular disease whose lung disease was not severe enough to warrant inclusion in the discharge summary as a primary or secondary diagnosis would be harmful.

Suissa and Ernst are correct to highlight the limitations of our observational study. However, the systematic withholding of β blockers from patients with COPD is not supported by published data, and we found no evidence of harm even among this inpatient population. Our results highlight the need for a randomised trial in the outpatient setting to definitively examine this issue.

M T Dransfield, S M Rowe, J Johnson, W Bailey, L Gerald

University at Alabama at Birmingham and the Birmingham VA Medical Centre, Birmingham, Alabama, USA

Correspondence to: Dr M T Dransfield, University at Alabama at Birmingham and the Birmingham VA Medical Centre, 215 THT 1900 University Blvd, Birmingham, AL 35294, USA; mdransfield99@msn.com

Competing interests: None declared.

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Predicting development and progression of COPD

Albers and colleagues[1] recently concluded that "Lung function below the normal range and early respiratory signs predict the development and progression of COPD". We have some concerns about the data. Table 2 in their article lists 151 subjects