How safe are anticholinergics in patients with COPD?

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Guidance for clinicians on how to interpret conflicting evidence from recent studies

Patients with advanced chronic obstructive pulmonary disease (COPD) have profound functional impairment and increased mortality.[1] Inhaled bronchodilators, including the anticholinergic agents tiotropium bromide and ipratropium bromide, relieve symptoms and improve lung function and quality of life. Tiotropium also reduces COPD exacerbations and hospitalisations.[2]

Recently, the safety of anticholinergics in patients with COPD has been questioned. Based on a pooled analysis provided by the manufacturers, the United States Food and Drug Administration (FDA) alerted clinicians to an increased risk of stroke with tiotropium.[3] Furthermore, a meta-analysis by Singh and colleagues[4] and a nested case–control study by Lee and colleagues[5] have reported an increased risk of cardiovascular events and death in patients taking inhaled anticholinergics.

Two background issues are relevant. First, with once-daily tiotropium, an improvement in lung function is maintained over time, whereas the respiratory effects of ipratropium wear off within 6 hours of each dose. It is therefore likely that their physiological effects outside the respiratory system are different. Also, the potential for overuse is greater with ipratropium, when taken as needed for symptom relief. Second, the presence of COPD is itself associated with an increased risk of cardiovascular death.[6] Reasons for this are incompletely understood and controversial. Furthermore, except for long-term oxygen, no medications for treating COPD clearly improve survival. A recent study suggesting improved survival with inhaler treatment was not designed to answer this question and its results require confirmation.[7]

The meta-analysis by Singh et al (some results of which have recently been revised in a published correction[4]) studied 17 randomised controlled trials in which cardiovascular events were reported and that involved 13 645 patients in whom either anticholinergics (ipratropium or tiotropium) or control therapies were used for at least 30 days.[4] It included data not available in previous meta-analyses. The primary outcome was a composite of cardiovascular death, myocardial infarction or stroke. This was more prevalent in the anticholinergic group, with a relative risk of 1.60 (95% CI, 1.22–2.10) and a risk difference of 0.007 (95% CI, 0.003–0.013). The secondary outcome was all-cause mortality, which was not statistically different between the two groups (the revised value given in the correction to the original study [$P = 0.05$] approaches, but does not reach, statistical significance).

The nested case–control study by Lee et al used national databases to identify 32 130 cases (patients with COPD who died) and 10 times that number of controls (surviving patients with COPD) in the US.[5] It showed an association of ipratropium use with both all-cause mortality (odds ratio [OR], 1.11; 95% CI, 1.08–1.15) and cardiovascular death (OR, 1.34; 95% CI, 1.22–1.47). Tiotropium was not examined in this study.

Coincidentally, results of the largest and longest-running randomised controlled trial of tiotropium use — the UPLIFT trial — have also recently been published.[8] This was a 4-year study investigating the clinical benefit of tiotropium and decline in lung function in 5993 patients with COPD. It found that in patients treated with tiotropium, there was no increase in cardiovascular death or stroke, myocardial infarction was less frequent, and there was a non-significant trend to lower all-cause mortality. These findings are in keeping with a meta-analysis conducted in 2006[2] and a large population study in 2007,[9] but the prospective nature of the UPLIFT study gives it greater validity.

How can these very different results be explained? Methodological weaknesses and differences in study design are probably a major factor. First, cardiovascular events and strokes were not defined a priori in any of the studies, raising the possibility of inaccurate data collection. In this setting, all-cause mortality is likely to be more reliable. Second, both the UPLIFT trial and Singh et al reported very high discontinuation rates. A third methodological weakness is the presence of confounders; for example, Lee et al's study was not able to eliminate or adjust for the crucial confounders of COPD severity and smoking status. Finally, study populations differed. In the UPLIFT study, the rate of ongoing

smoking was low and the use of other concurrent COPD medication probably higher than in most of the studies analysed by Singh et al — both these factors may be cardioprotective.

How does one act on this conflicting and partially flawed safety data? Regarding tiotropium specifically, no study has shown an increase in all-cause mortality. In the studies performed so far, all-cause mortality is likely to be a more robust outcome than death due to cardiovascular or respiratory causes. Even if the increase in cardiovascular events with tiotropium reported by Singh et al is correct, the size of the effect is small, and the unchanged all-cause mortality suggests that another specific cause of death has decreased. Singh et al did not report respiratory deaths, but some other studies have shown a decrease in these with tiotropium use,[9] consistent with its beneficial effects on exacerbations and hospital admissions.[8]

The safety of ipratropium is less clear. The concerns raised by Singh et al are reinforced by Lee et al's finding of increased all-cause and cardiovascular mortality with ipratropium use.

No guidelines have yet incorporated these recent studies into their recommendations, and the FDA's response based on its ongoing safety review is pending. In the interim, the use of tiotropium in patients with COPD is likely to be safe and beneficial. If a short-acting bronchodilator is desired, the cardiac risk profile of the patient must be considered because of the uncertain safety of both ipratropium and short-acting β_2 agonists.[10] Finally, the uncertainty about the safety of anticholinergics needs to be placed in the context of managing patients whose COPD presents major challenges related to their severe respiratory impairment and the increased risk of comorbidities such as lung cancer, depression and osteoporosis, as well as cardiovascular disease.

Competing interests

Mark Hew received travel assistance from AstraZeneca and Altana to attend three conferences in 2004–2005. Louis Irving has in the past received support from GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim to attend American and European Respiratory Society meetings and industry-supported educational meetings in Australia.

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