LETTER TO THE EDITOR

Response to Ringbaek et al.

Ringbaek and Viskum (p. 271) concluded recently: "our results support a relationship between ipratropium and premature death in patients with obstructive lung disease." Several points made by the authors, however, raise questions as to whether the results truly support this conclusion:

- Our patients who were given ipratropium were more severe than those who were not. (p. 269)
- Ipratropium users were more frequently prescribed prednisolone. Our adjustment for use of prednisolone as "yes" or "no" may not provide a fully sufficient adjustment for the differences in this marker of severity and risk of death. (p. 270)
- The increased mortality of all causes observed in patients with inhaled ipratropium was derived from an increased risk of COPD death, and lung cancer death. (p. 266–7)
- We cannot rule out bias due to unmeasured confounding; e.g., residual confounding by disease severity. (p. 269)
- An increased risk of dying from cancer was observed among our COPD patients with ipratropium. The most likely explanation for this association is residual confounding from tobacco smoking. (p. 270–1)

Because patients with more severe respiratory disease are more likely to die from their respiratory disease, the finding that ipratropium was prescribed preferentially to patients with more severe respiratory disease is noteworthy. Taken together, one would expect in this study that patients who received ipratropium would have increased mortality from respiratory disease. Accordingly, the key findings are that patients who received ipratropium died more frequently from lung cancer and COPD. The authors attribute increased lung cancer mortality to uncontrolled effects of smoking. A similar association with COPD mortality, however, is attributed by the authors to the medication. We suggest that that the same uncontrolled risk factors that caused increased lung cancer mortality in this study also caused increased mortality from COPD.

It should not be surprising that nonrandomized studies find various respiratory drugs are associated with increased respiratory mortality. Separating possible effects of drugs from effects of underlying disease remains a most challenging interpretive issue in these studies, and highlights the importance of clinical endpoints in randomized studies. Ipratropium is one of few respiratory drugs for which a large randomized study has corroborated the absence of a relation with increased mortality. These results provide reassurance that, insofar as ipratropium is concerned, it is not the drug but rather smoking and COPD that increase mortality.

References


S. Lanes
Boehringer Ingelheim, Pharmaceuticals, Inc. 900 Ridgebury Road, Ridgefield, CT 06877-0368, USA