Rebuttal: Should we avoid β-agonists for moderate and severe chronic obstructive pulmonary disease?

YES

Shelley R. Salpeter MD FACP

Dr Aaron has accurately outlined the beneficial effects of β-agonist use on lung function in patients with chronic obstructive pulmonary disease (COPD). It is important to point out that anticholinergic agents, such as ipratropium and tiotropium, are equally effective bronchodilators for COPD. Anticholinergics, however, have been shown to reduce respiratory mortality substantially compared with placebo, while some evidence suggests that β-agonists might actually increase respiratory mortality. In our recent meta-analysis we pooled all the data on respiratory deaths available to us at the time, after contacting the investigators of the trials to obtain unpublished information. When a subsequent letter to the editor reported that duplicate data had been provided for 2 of the published trials, we reanalyzed the data with the duplicate data excluded, and there was still a statistically significant twofold increase in respiratory mortality for β-agonists compared with placebo.[1]

The TORCH (Towards a Revolution in COPD Health) trial has recently been published,[2] and it is true that it showed a nonsignificant trend toward reduced total mortality in the salmeterol group compared with the placebo group. Dr Aaron failed to note, however, that there was actually an increase in COPD deaths and respiratory deaths in the salmeterol group compared with the placebo group, although this did not reach statistical significance. If the TORCH data were added to the pooled data on β-agonist use for COPD, there would still be an increase in respiratory mortality for β-agonists compared with placebo, although the results might not reach statistical significance any more. This is in stark contrast with the pooled data on anticholinergic agents that show a statistically significant 70% ($P=.02$) reduction in respiratory deaths compared with placebo.[3] Trials that have directly compared the 2 types of bronchodilators have shown a statistically significant fivefold increase in total mortality with β-agonists compared with anticholinergics.[4] This indicates that anticholinergic agents

NO

Shawn D. Aaron MD

Dr Salpeter argues that monotherapy with β-agonists might be dangerous for patients with asthma. This could be true; however, the question being debated concerns β-agonist use for chronic obstructive pulmonary disease (COPD), not for asthma. Many large clinical trials and properly done meta-analyses[1] have confirmed that β-agonists are extremely effective at improving lung function, relieving dyspnea, improving quality of life, and preventing exacerbations among patients with COPD.[2,3] Recent large clinical trials have also confirmed that β-agonists are safe for patients with COPD.

The 1 meta-analysis that diverges from all of the rest is the meta-analysis done by Dr Salpeter.[4] This meta-analysis had serious flaws. Only 4 published trials studying β-agonists were included, even though more than 15 trials were available in the literature. Furthermore, the authors did not attempt to obtain mortality data from many of the pivotal randomized controlled trials published on this subject. The 4 trials included in the meta-analysis contained duplicate publications. Sixty percent of the results of the Salpeter meta-analysis came from the results of only 1 study. The results of this meta-analysis are simply unreliable.

The TORCH (Towards a Revolution in COPD Health) trial, a randomized double-blind placebo-controlled clinical trial, unequivocally showed that 1521 COPD patients treated with the long-acting β-agonist salmeterol for 3 years had a slightly greater (but not statistically significant) chance of survival over 3 years than 1524 patients treated with placebo had (hazard ratio 0.88, 95% confidence interval [CI] 0.73 to 1.06).[5] Many more patients were included in the TORCH trial then were included in the entire Salpeter meta-analysis of 4 studies. In addition, patients treated with fluticasone-salmeterol combination products showed a 3-year survival benefit compared with patients given placebo (hazard ratio 0.83, 95% CI 0.68 to 1.00). Patients treated with either salmeterol or fluticasone-salmeterol combinations had improved lung

These rebuttals are responses from the authors who were asked to discuss whether β-agonists should be avoided for moderate and severe chronic obstructive pulmonary disease in the Debates section of the August issue (*Can Fam Physician* 2007;53:1290-3 [Eng], 1294-7 [Fr]).

YES

should be the drugs of choice to achieve safe and effective bronchodilation for patients with COPD.

References

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NO

function, improved quality of life, and 15% to 25% fewer exacerbations than those treated with placebo. Therefore long-acting β-agonists and inhaled steroid–long-acting β-agonist combination products appear to improve lung function and quality of life, decrease exacerbations, and also slightly improve survival. They unquestionably do not kill people with COPD!

References

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