EDITORIAL

The use of inhaled anticholinergics in chronic obstructive pulmonary disease

Is there cause for concern of cardiovascular safety?

R. Andrew McIvor

Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Correspondence to:
R. Andrew McIvor, MD, MSc, FRCP, Firestone Institute for Respiratory Health, St. Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, ON, L8N 4A6, Canada, phone: +1-905-522-11-55, fax: +1-905-521-61-83, e-mail: amcivor@stjosham.on.ca
Received: October 14, 2009.
Accepted: October 23, 2009.
Conflict of interest: R.A. McIvor has received honoraria for providing continued medical education and attending advisory board meetings of pharmaceutical companies involved in COPD management including AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKlein, Nycomed, and Pfizer.
Pol Arch Med Wewn. 2009; 119 (11): 697-698

Introduction Although a previous pooled analysis of 19 short-term placebo-controlled trials revealed no significant increase in the risk of cardiovascular (CV) adverse events with tiotropium bromide,[1] two recent publications, a nested case-control study[2] and a systematic review with meta-analysis[3] reported an increased risk for all-cause and CV mortality, myocardial infarction (MI), and stroke in patients with chronic obstructive pulmonary disease (COPD) who received tiotropium or short-acting inhaled anticholinergics, two common medications widely prescribed for COPD.

What started the controversy of increased cardiac events and anticholinergics? Singh et al. reported a systematic review and meta-analysis of ipratropium and tiotropium, focusing on the cardiovascular safety of these drugs.[3] They included 17 randomized controlled trials (RCTs) encompassing 13,645 patients and lasting between 6 weeks and 5 years. Some of the trials were published while others were unpublished and obtained from government and corporate sources.

The team's analysis of all 17 studies showed that inhaled anticholinergics were associated with a 1.9% risk of the primary endpoint (a composite of cardiovascular death, and nonfatal MI and stroke), while control therapy was associated with a 1.2% risk (relative risk [RR] 1.6; 95% confidence interval [CI] 1.22–2.1, P <0.001).

A nested case-control study by Lee et al. yielded similar findings.[2] The study involved 32,130 newly diagnosed patients and 320,501 control participants from the U.S. Veterans Affairs healthcare system. The adjusted odds ratios (OR) for all-cause mortality were 0.80 (95% CI 0.78–0.83) for inhaled corticosteroids, 1.11 (95% CI 1.08–1.15) for ipratropium, 0.92 (95% CI 0.88–0.96) for long-acting β_2-agonists and 1.05 (95% CI 0.99–1.10) for theophylline. Ipratropium was associated with an increased risk for cardiovascular death (OR 1.34; 95% CI 1.22–1.47).

Update of literature Since our recent editorial in this journal,[4] three new publications have been made available in the peer-reviewed literature addressing this conundrum, especially as it applies to tiotropium bromide. Celli et al.[5] reports on an update of the clinical trial safety database for tiotropium principally by augmentation of previous information with data from a 4-year trial in COPD (UPLIFT).[6] Rodrigo et al. reports a systematic review and meta-analysis of the same drug[7] and Salpeter reports a review of the current data and pooled analysis.[8]

What is the new information? Rodrigo et al. performed systematic searches in MEDLINE, EMBASE, the Cochrane Controlled Trials Register, manufactures' trial register, and Food and Drug Administration databases, without language restriction. Primary outcomes were a composite of major adverse cardiovascular events (cardiovascular mortality, and nonfatal MI or stroke during the treatment period). RRs were estimated using fixed-effects models and statistical heterogeneity was estimated with the I^2 statistic.

Their main results included 19 randomized controlled trials (18,111 participants). There was no difference in the incidence of adverse cardiovascular events (RR 0.96; 95% CI 0.82–1.12, I^2 6%). Among individual components of the composite outcome, tiotropium did not significantly increase the risk of cardiovascular death (RR 0.93; 95% CI 0.73–1.20, I^2 1%), nonfatal MI (RR 0.84; 95% CI, 0.64–1.09, I^2 0%), and nonfatal stroke (RR 1.04; 95% CI 0.78–1.39, I^2 0%). A smoking history of more than 55 pack years presented

a trend to a higher rate of cardiovascular adverse events in patients receiving tiotropium.

They concluded that compared with control (placebo or salmeterol), tiotropium did not significantly increase the risk of adverse major cardiovascular events among COPD patients. A subgroup analysis suggested that smoking history can modify the risk of cardiovascular adverse events.

Celli et al. included trials with the following criteria: lasting 4 weeks or longer, randomized, double-blind, parallel-group, placebo-controlled. Inclusion/exclusion criteria were similar including spirometry-confirmed COPD, a smoking history of 10 or more pack years, age 40 years or older. Incidence rates (IR) were determined from the total number of patients with an event divided by total time at risk. Rate ratios and 95% CI for tiotropium/placebo were calculated. IR were determined for all-cause mortality and selected CV events including a composite CV endpoint encompassing CV deaths, nonfatal MI, nonfatal stroke, and the terms "sudden death", "sudden cardiac death", and "cardiac death".

The main results from 30 trials including 19,545 patients randomized to receive triotropium (n = 10,846) and placebo (n = 8699) were evaluated. Mean forced expiratory volume in 1 second was 1.15 ±0.46 l (41 ±14% predicted), 76% men, mean age was 65 ±9 years. Cumulative exposure to study drug was 13,146 (tiotropium) and 11,095 (placebo) patient-years. For all-cause mortality, the IR was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years [RR (95% CI) = 0.88 (0.77, 0.999)]. IR for the CV endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years [RR (95% CI) = 0.83 (0.71, 0.98)]. The IR for the CV mortality excluding nonfatal MI and stroke was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years [RR (95% CI) = 0.77 (0.60, 0.98)]. For total MI, cardiac failure and stroke the RRs (95% CI) were 0.78 (0.59, 1.02), 0.82 (0.69, 0.98), and 1.03 (0.79, 1.35), respectively.

They concluded that tiotropium was associated with a reduction in the risk of all-cause mortality, cardiovascular mortality, and serious cardiovascular events.

Salpeter reports a synthesis of the available evidence and in her review discusses that although the meta-analysis of randomized trials observed that a higher proportion of participants receiving inhaled anticholinergics had major cardiovascular events compared with those receiving placebo, this differential is eliminated when the large UPLIFT trial is included in the meta-analysis or when evaluating the rate of events per total person-years of exposure. In fact, updated pooled trial data indicate that tiotropium bromide may actually reduce the incidence rates of major cardiovascular events and total mortality over time.

Conclusion In conclusion, there have been conflicting data concerning the cardiovascular risk associated with the inhaled anticholinergic agents, ipratropium bromide and tiotropium bromide. Observational studies and some randomized trials have shown an increase in adverse CV events, whereas pooled data (particularly with inclusion of UPLIFT data) from all available trials show no significant effect on the proportion of patients with adverse CV events and a trend towards reduced incidence of events over time. It is worth remembering, however, that none of these studies had cardiovascular outcomes as the primary outcome.

It is also important to remember that COPD patients have a high risk of cardiovascular events, probably because of shared CV risk factors and underlying systemic inflammation along with the significant numbers of these individuals who continue to smoke during the observation period. In patients with COPD, hospitalizations and deaths are more often due to CV causes than respiratory events.

In balance, as this story evolves, all the updates and new evidence since my previous commentary on CV safety are very supportive as to the safety of the anticholinergic class.[4] I am reassured and remain comfortable with the position of anticholinergics both short- and long-acting within our national and international guidelines and in my day-to-day management of COPD.

REFERENCES

1 Kesten S, Jara M, Wentworth C, et al. Pooled clinical trial analysis of tiotropium safety. Chest. 2006; 130: 1695-1703.

2 Lee TA, Pickard AS, Au DH, et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med. 2008; 149: 380-390.

3 Singh S, Loke YK, Furberg CD, et al. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008; 300: 1439-1450.

4 Sindi A, McIvor A. The use of inhaled anticholinergics in chronic obstructive pulmonary disease: is there cause for concern? A review of evidence from clinical trials. Pol Arch Med Wewn. 2009; 119: 74-78.

5 Celli B, Decramer M, Leimer I, et al. Cardiovascular Safety of Tiotropium in Patients With COPD. Chest. 2009 Jul 10. [Epub ahead of print].

6 Tashkin DP, Celli B, Senn S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008; 359: 1543-1554.

7 Rodrigo GJ, Castro-Rodriguez JA, Nannini LJ, et al. Tiotropium and risk for fatal and nonfatal cardiovascular events in patients with chronic obstructive pulmonary disease: systematic review with meta-analysis. Respir Med. 2009; 103, 1421-1429.

8 Salpeter SR. Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events? A synthesis of the available evidence. Drugs. 2009; 69: 2025-2033.