Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials

Singh S, Loke YK, Enright PL, Furberg CD

CRD summary
The authors concluded that there was a 52% increased risk of mortality associated with the tiotropium mist inhaler in patients with chronic obstructive pulmonary disease. This was a well-conducted review and the conclusion is likely to be reliable.

Authors' objectives
To evaluate the risk of mortality following long-term use of tiotropium delivered using a mist inhaler in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE and EMBASE were searched from inception to July 2010 for studies in any language. Unpublished studies were sought from the Boehringer Ingelheim clinical trials register, US Food and Drug Administration website and ClinicalTrials.gov to July 2010. Search terms were reported. Bibliographies of systematic reviews and included studies were scanned for further articles.

Study selection
Randomised controlled trials (RCTs) that compared use of a tiotropium mist inhaler (Respimat Soft Mist Inhaler, Boehringer Ingelheim) to placebo in patients with COPD were eligible for inclusion. The primary outcome was mortality from any cause. Trials had to report treatment duration for at least 30 days and provide numerical data on mortality.

The included trials were multinational trials that evaluated two doses of tiotropium (5µg and 10µg). Trial duration ranged from 12 weeks to one year. Most patients were male. Ages ranging from 63 to 65.7 years. Around one third of trialists were current smokers. Cardiovascular deaths were included as a secondary outcome.

Two reviewers independently carried out study selection. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed using Cochrane criteria of randomisation, allocation concealment, blinding, loss to follow-up and withdrawals. The quality of adverse events recording was assessed.

Two reviewers independently carried out the quality assessment. Disagreements were resolved by consensus.

Data extraction
Data were extracted to enable presentation of relative risks (RR) and 95% confidence intervals (CI). A continuity correction of 0.5 was added to trials with zero events in the placebo arm. Authors were contacted for data clarification, where necessary.

Two reviewers independently carried out data extraction. Disagreement were resolved by consensus.

Methods of synthesis
Relative risks and 95% CIs were pooled in a fixed-effect meta-analysis (Mantel-Haenszel model). Statistical heterogeneity was assessed using the $I^2$ statistic (>50% represented high variation). Sensitivity analyses were carried out using a random-effects model, Peto-odds ratio analysis and to explore the relative influence of drug dose, trial duration and addition of a trial that was not included in the meta-analysis. The number needed to treat (NNT) was calculated.
Results of the review
Five RCTs (n=6,522) were included in the meta-analysis. Trial quality was considered satisfactory. All studies reported adequate sequence generation or allocation concealment, double-blinding and clearly reported loss to follow-up (where necessary). Methods of adverse event monitoring was reported in all trials.

The tiotropium mist inhaler was significantly associated with an increased risk of mortality (RR 1.52, 95% CI 1.06 to 2.16; five trials); this result was driven by results from three 12-month trials. The tiotropium inhaler was associated with significantly increased mortality risks at doses of 5µg (RR 1.46, 95% CI 1.01 to 2.10; five trials) and and 10µg (RR 2.15, 95% CI 1.03 to 4.51; four trials). There was no evidence of statistical heterogeneity in any of the analyses.

Sensitivity analyses did not materially alter the main findings. The annualized NNT was 124 (one excess death likely from every 124 patients treated with the 5µg tiotropium inhaler over one year).

Risk of cardiovascular death was significantly increased following use of the inhaler (RR 2.05, 95% CI 1.06 to 3.99, I² = 0%; four trials).

Authors’ conclusions
There was a 52% increased risk of mortality associated with the tiotropium mist inhaler in patients with COPD.

CRD commentary
The review question was clear and inclusion criteria were sufficiently reproducible. The search strategy included relevant sources of published and unpublished data, and attempts were made to minimise language bias. Trial quality was assessed using a recognised assessment tool and the results indicated good methodological standards. Study details were presented, statistical heterogeneity was assessed, the chosen method of synthesis was appropriate and sensitivity analyses were carried out. The authors drew attention to on-going trial.

The authors’ recommendations for practice and research seemed to be justified by the evidence presented. This was a well-conducted review and the conclusion is likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that clinicians should prescribe cautiously and inform patients (particularly those with underlying cardiac disease) of the increased risk of mortality associated with the tiotropium mist inhaler.

Research: The authors stated that future trials should evaluate the effects of long-acting inhaled anticholinergics on cardiovascular events and mortality in patients with high risk factors typically excluded from trials (for example, pre-existing arrhythmias, cardiomegaly and moderate to severe renal impairment).

Funding
National Center for Research Resources, National Institutes of Health, UK, grant number 1KL2RR025006-03; National Institutes of Health Roadmap for Medical Research.

Bibliographic details

PubMedID
21672999

DOI
10.1136/bmj.d3215
Original Paper URL
http://www.bmj.com/content/342/bmj.d3215.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Bronchodilator Agents /administration & dosage /adverse effects /therapeutic use; Humans; Pulmonary Disease, Chronic Obstructive /drug therapy /mortality; Randomized Controlled Trials as Topic; Scopolamine Derivatives /administration & dosage /adverse effects /therapeutic use; Tiotropium Bromide

AccessionNumber
12011003667

Date abstract record published
22/06/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.