Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies

Loke YK, Cavallazzi R, Singh S

CRD summary
This review concluded that long-term exposure to inhaled fluticasone and budesonide had a modest significant association with an increased risk of fracture among chronic obstructive pulmonary disease patients and suggested the presence of a dose-response effect. Conclusions on the fracture risk associated with fluticasone seem reliable. Conclusions on budesonide should be treated with caution due to limited evidence.

Authors' objectives
To evaluate the risk of fractures associated with long-term use of inhaled corticosteroids compared with control treatments in patients with chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE and EMBASE searches from an earlier review were updated to August 2010. There were no language restrictions. Search terms were reported. Websites of regulatory authorities, trials registers, references of reviews and included articles were searched.

Study selection
Randomised controlled trials (RCTs) and controlled observational studies of patients with COPD that reported outcome data on fracture adverse events were eligible for inclusion. Studies were required to report odds ratios (ORs), risk ratios or hazard ratios, or sufficient data to enable calculation of odds ratios.

RCTs were eligible if the intervention included fluticasone or budesonide and if comparison groups consisted of inhaled corticosteroids versus placebo or inhaled corticosteroids plus long-acting β2-agonist (LABA) versus LABA alone. Observational studies were eligible if they included comparisons between any inhaled corticosteroids exposure versus no exposure. Studies that evaluated inhaled corticosteroid use in acute COPD exacerbations and RCTs that lasted less than 24 weeks were excluded. Trials with mixed asthma/COPD patients were excluded if they did not report separate outcome data for COPD patients.

Fewer than half of the patients were male in all the RCTs and in four of the seven observational studies. Trial participants were on average 60 to 70 years old and tended to have severe COPD. The types of inhaled corticosteroids used varied; most studies evaluated fluticasone. Trials had a mean duration of 90 weeks (range 24 to 154 weeks).

Two reviewers independently selected studies for inclusion in duplicate.

Assessment of study quality
Blinding, allocation concealment, withdrawals and loss to follow-up were assessed in RCTs. Ascertainment of exposure and outcomes, information on participant selection and methods to address confounding were assessed in observational studies.

Two reviewers independently assessed study quality.

Data extraction
Odds ratios (OR) of fracture adverse events and 95% confidence intervals (CIs) were extracted or calculated. Beclomethasone equivalents were calculated for observational studies. Authors were contacted for data clarification where necessary.

Two reviewers independently extracted data. Disagreements were resolved with a third reviewer.

Methods of synthesis
Data on fracture incidence was pooled using Peto odds ratios with 95% CI. The effects of different control comparators
and alternative synthesis models were tested in pre-specified sensitivity analyses. The effects of trial quality and duration were tested in a posteriori (identified during the review process) sensitivity analyses. Odds of fracture were pooled and stratified by predefined subcategories of inhaled corticosteroids exposure in observational studies.

The number needed to harm (NNH) and 95% CI were calculated by applying the odds ratio estimates to the control event rate. A dose-response analysis was conducted with a variance-weighted least squares meta-regression in six observational studies. Heterogeneity was assessed using I². Publication bias was analysed with a forest plot.

**Results of the review**

Sixteen RCTs (17,513 participants) and seven observational studies (69,000 participants) (five nested case controls and two cross-sectional studies) were included in the meta-analyses. The quality of the RCTs was variable: seven RCTs had low risk of bias and the other nine had gaps in the reporting of some methodological aspects. Several potentially important methodological limitations were reported in the observational studies. The funnel plot suggested no significant risk of publication bias for the RCTs.

Fluticasone (14 trials) and budesonide (two trials) were associated with a significantly increased risk of fractures: 180 of 9,143 (2.0%) for the intervention versus 141 of 8,370 (1.7%) for control (Peto OR 1.27, 95% CI 1.01 to 1.58; 16 RCTs). Inhaled corticosteroid exposure was associated with a significantly increased risk of fractures (OR 1.21, 95% CI 1.12 to 1.32; seven observational studies) in the observational studies. No significant heterogeneity was identified between the RCTs (I²=0) and between the observational studies (I²=37%).

Subgroup analyses pooled trials that compared inhaled corticosteroids alone versus placebo showed no significant between-group difference in risk of fractures (Peto OR 1.19, 95% CI 0.86 to 1.64; 10 RCTs, 7,704 participants), but showed an increased risk for patients treated with inhaled corticosteroids plus LABA versus LABA alone that was close to being statistically significant (1.34, 95% CI 0.99 to 1.82; 11 trials, 9,809 participants).

Results from the meta-analysis of observational studies according to exposure subcategories were consistent. Each 500μg beclomethasone dose equivalent was associated with a 9% increased risk in fractures (OR 1.09, 95% CI 1.06 to 1.12; seven observational studies).

**Authors' conclusions**

Long-term exposure to inhaled fluticasone and budesonide had a modest but significant association with an increased risk of fracture among COPD patients. Higher doses were associated with a greater risk of fracture, which suggested the presence of a dose-response effect.

**CRD commentary**

The review question and inclusion criteria were clear. The literature search was thorough. Study details were generally well reported, although outcomes associated with specific inhaled corticosteroids drugs were not reported in the observational studies. Validity of the included studies and overall strength of evidence were assessed appropriately and the results were used in the synthesis. Seven of the 18 RCTs had low risk of bias. The quality of some of the other nine RCTs was unclear due to gaps in the reporting of the primary studies and in the observational studies some potentially important methodological flaws were identified, which may limit the reliability of the evidence.

Appropriate statistical analyses were conducted. Risk estimates were adjusted for concomitant medication for the observational studies, but not for the RCTs, despite higher oral corticosteroid exposure being documented in several of the control groups. This may limit the reliability of the pooled estimate from the trials. The evidence on budesonide was limited in the trials and there was no separate report of outcomes associated with individual inhaled corticosteroids drugs in the observational studies.

Results on the risk associated with budesonide exposure should be interpreted with caution. Conclusions on the fracture risk associated with fluticasone use seem reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the relative increase in fracture risk should be weighted against the relative reduction in COPD exacerbations. They also stated that bone protective drugs may be warranted in vulnerable patient groups.
Research: The authors stated that the precise location of the fractures should be evaluated, that future studies should assess whether fracture risk varies with COPD severity and whether concomitant bone-protective drugs can reduce this risk. The authors noted that trials should include a larger proportion of postmenopausal women and that the risk of fractures associated with the newer formulations of inhaled corticosteroids should be assessed. They stated that the dose-response link with efficacy and safety should be carefully evaluated to optimise dose prescription.

Funding
National Center for Research Resources, USA; John Hopkins Clinical Research Scholars Program

Bibliographic details

PubMedID
21602540

DOI
10.1136/thx.2011.160028

Original Paper URL
http://thorax.bmj.com/content/66/8/699.abstract

Additional Data URL
http://thorax.bmj.com/content/66/8/699/suppl/DC1

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Aged; Androstadienes /administration & dosage /adverse effects; Budesonide /administration & dosage /adverse effects; Dose-Response Relationship, Drug; Female; Fluticasone; Fractures, Bone /chemically induced; Glucocorticoids /administration & dosage /adverse effects; Humans; Male; Middle Aged; Pulmonary Disease, Chronic Obstructive /drug therapy; Randomized Controlled Trials as Topic; Risk Assessment /methods

AccessionNumber
12011004995

Date bibliographic record published
02/11/2011

Date abstract record published
25/01/2012

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.