Impact of inhaled corticosteroid-induced oropharyngeal adverse events: results from a meta-analysis

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CRD summary
This review assessed oropharyngeal adverse events associated with corticosteroid inhalation in participants with persistent asthma. The authors concluded that inhaled corticosteroids can be associated with oropharyngeal adverse events; these may be reduced by post-dose mouth rinsing or the use of spacers. Despite the methodological problems of the review, the first part of the conclusion appears to be consistent with the data presented.

Authors' objectives
To assess the risk of inhaled corticosteroid (ICS)-induced oral candidiasis, dysphonia and pharyngitis among currently available therapies, and to determine associated effects of dose and device.

Searching
MEDLINE (January 1966 to June 2004) and EMBASE (January 1974 to June 2004) were searched; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion. Only studies reporting appropriate information on study design were included.

Specific interventions included in the review
To be eligible, studies had to investigate ICS as a therapy for persistent asthma as single or combination therapy compared with placebo. The included studies investigated ICS delivered by a dry powder inhaler (DPI) or metered-dose inhaler (MDI) as follows: fluticasone propionate (mainly DPI, some MDI), triamcinolone acetonide (all MDI), budesonide (mainly DPI, two MDI), beclometasone dipropionate (all MDI), and mometasone furoate (mainly DPI, some MDI).

Participants included in the review
Studies of adolescents or adults with persistent asthma of all severities were eligible for inclusion; patients with chronic obstructive pulmonary disease were excluded. Only studies reporting appropriate information on patient demographics were included, but these were not reported.

Outcomes assessed in the review
Studies were eligible if they reported on at least one of the following outcomes: incidence of oral candidiasis, dysphonia or pharyngitis (sore throat or throat irritation).

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The reviewers recorded whether the studies were single- or double-blind. The authors did not state how the validity assessment was performed.

Data extraction
The reviewers extracted the outcomes to calculate odds ratios (ORs). The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
How were the studies combined?
Study results were depicted in box plots and summary estimates were derived from logistic regression models.

How were differences between studies investigated?
The incidence rates of oropharyngeal adverse events were classified by ICS type, dose (low, less than 400 microg; medium, 401 to 999 microg; high, more than 1,000 microg), device (MDI or DPI) and propellant (chlorofluorocarbon or hydrofluoroalkane). Poisson and logistic regressions were used to evaluate dose-dependent trends in the incidence of oropharyngeal adverse events.

**Results of the review**
Twenty-three studies (at least 4,238 participants; exact number unclear) were included in the review.

All of the studies were double-blind except for one, which was single-blind. Six of the studies had adequate allocation concealment; for the rest, allocation concealment was unclear.

ICS at all doses and regardless of device were associated with a significantly greater incidence of oral candidiasis (OR 3.6, p<0.001; 20 studies), dysphonia (OR 5.2, p<0.001; 15 studies), and pharyngitis (OR 2.2, p<0.023; 16 studies) than placebo.

Compared with placebo and regardless of dose or device, fluticasone propionate had the greatest risk of oral candidiasis (OR 5.41, p<0.001) while budesonide had the greatest risk of both dysphonia (OR 11.45, p=0.02) and pharyngitis (OR 5.09, p=0.04).

The MDI device was associated with a 5-fold greater risk of oral candidiasis compared with placebo (OR 5.40), whereas the DPI device only showed a 3-fold greater risk of oral candidiasis compared with placebo (OR 3.24). Trends for dysphonia were similar (OR 5.68 and OR 3.74 for MDI and DPI, respectively). The risk for dysphonia was increased 2-fold when using either device.

**Authors' conclusions**
Currently available ICS can be associated with oropharyngeal adverse events; these may be reduced by post-dose mouth rinsing or the use of spacers.

**CRD commentary**
This review had clearly stated inclusion criteria. The search was limited: only two databases were searched and searches for unpublished data were not conducted. Relevant studies may therefore have been missed and publication bias may have been introduced into the review. No efforts were made to obtain supplementary information, which might have been relatively easy to obtain given that the authors had a link to some of the companies producing the relevant drugs. Details of the review methods such as the study selection, validity assessment and data extraction procedures were not presented, making it difficult to evaluate the quality of the review. Only limited aspects of the quality of the included studies were reported. Patient characteristics and the numbers of patients in the studies were not reported. The method used to pool results was not further described, which is especially unfortunate since no standard meta-analytic technique was used and it is unclear whether any form of weighting was applied. No heterogeneity assessment was carried out and no systematic statistical data were reported for the regression and subgroup analyses.

All but one of the included studies had study durations of no longer than 4 months, which appears inadequate for assessing adverse events of a regularly used treatment for a chronic condition, and adverse event rates in the longer term may be higher than the ones quoted.
The authors suggest in their conclusions that oropharyngeal adverse events of ICS may be reduced by the use of a spacer or post-dose mouth rinsing, but no systematic data to substantiate this claim were reported. Despite the methodological problems of this review, the first part of the conclusion appears to be consistent with the data presented.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

**Bibliographic details**

**Other publications of related interest**
This additional published commentary may also be of interest. Cicutto L. Review: inhaled corticosteroids increase risk of oral candidiasis, dysphonia, and pharyngitis in persistent asthma. Evid Based Nurs 2007;10:109.

**Indexing Status**
Subject indexing assigned by NLM

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