Inhaled ciclesonide versus inhaled budesonide or inhaled beclomethasone or inhaled fluticasone for chronic asthma in adults: a systematic review

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CRD summary
This review evaluated ciclesonide and alternative inhaled corticosteroids for asthma in adults. It concluded that there is limited evidence that inhaled ciclesonide has similar effectiveness and efficacy to fluticasone and budesonide, but no clear evidence on side-effects. The conclusions about limited evidence seem reliable; further data may become available when identified studies reported as abstracts are published in full.

Authors' objectives
To review published randomised controlled trials (RCTs) of the effectiveness and safety of inhaled ciclesonide in comparison with alternative inhaled corticosteroids in adults with asthma.

Searching
MEDLINE (via PubMed) (from 1951), EMBASE, the Cochrane Library and six relevant internet sites (e.g. Drug and Therapeutics Bulletin, Canadian Coordinating Office for Health Technology Assessment) were used to identify studies. The reference lists of retrieved articles were screened. The search terms, but not the end search date, were reported and no language restrictions were applied. Studies published as abstracts were only included if they reported sufficient information to permit a validity assessment.

Study selection
Study designs of evaluations included in the review
RCTs and systematic reviews published in or after 2004 were eligible. None of the included studies was a parallel trial.

Specific interventions included in the review
Studies comparing the inhalation of ciclesonide with that of budesonide, beclomethasone or fluticasone were eligible for inclusion. Studies on oral, nasal or intravenous administration were excluded, as were studies that compared ciclesonide treatment with placebo only or asthma treatments other than the mentioned comparators. The included studies compared the administration of ciclesonide (400 microg once daily or 800 microg once or twice daily) with the administration of budesonide (400 or 800 microg daily; given in a turbohaler), or fluticasone (250 or 1000 microg once or twice daily). None of the included studies compared ciclesonide with beclomethasone.

Participants included in the review
Studies including adults (18 years and over) with a diagnosis of chronic asthma were eligible. Patients with acute asthma, chronic obstructive pulmonary disease or allergic rhinitis were excluded. The patients in the included studies had a mean age of 33 to 47 years, not all studies were in non-smoker samples only, and more than half of the studies involved participants with mild asthma (forced expiratory volume in 1 second less than 90% of predicted value).

Outcomes assessed in the review
The review considered all reported outcomes with an emphasis on patient outcomes. The included studies assessed lung function tests (e.g. FEV1, FVC, PEF), symptoms (diary and use of rescue medication), quality of life (Mini Asthma Quality of Life questionnaire), airway responsiveness to provoking agents (adenosine monophosphate or metacholine until a 20% reduction in FEV1 is reached), inflammatory markers (nitric oxide exhaled, inflammatory markers in sputum), hypothalamic-pituitary-adrenal suppression (plasma cortisol response to human corticotropin-releasing factor, urine cortisone) and oropharyngeal deposition. The duration of the study, which also determined the follow-up measurement, ranged from measurements up to 60 minutes after the intervention to a maximum of 4 weeks.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the studies. Any disagreements were resolved through discussion.
Assessment of study quality
Two reviewers independently assessed allocation concealment, blinding, the method of randomisation, attrition, balance at baseline and equal handling. Four trials were excluded because they contained insufficient detail for a critical appraisal of methodological quality.

Data extraction
One reviewer extracted numerous study and treatment details from the included studies, including the source of funding. The results extracted included reported differences with 95% confidence intervals (CIs) between treatments or changes from baseline.

Methods of synthesis
How were the studies combined?
The trials were combined in a narrative review with accompanying tables.

How were differences between studies investigated?
Differences between the trials were highlighted in the narrative review.

Results of the review
Five RCTs (84 completers) were included: 3 cross-over trials (n=48) and 2 within-patient trials (n=36) that reported outcomes up to 60 minutes after treatment.

One trial was clearly double-blind, two reported that inhalers were masked to the patient, and none reported the method of allocation concealment or randomisation. The attrition rates varied from 5.2 to 30%, there was no evidence of performance bias, and 4 trials were sponsored by the drug companies manufacturing ciclesonide. The sample size ranged from 15 to 19.

None of the 5 trials reported any benefits of ciclesonide over budesonide or fluticasone regarding lung function (3 trials), symptoms (2 trials), quality of life (2 trials), airway responsiveness to a provoking agent (3 trials) or inflammatory markers (2 trials).

One trial reported that the combined deposition of ciclesonide and its metabolite in the oropharynx was 47% of that of budesonide; one trial reported that the combined deposition of ciclesonide and its active metabolite in the oropharynx was 54% of that of fluticasone. One trial reported less suppression of cortisol in overnight urine collection after ciclesonide compared with fluticasone (geometric mean fold difference 1.5, 95% CI: 1.1, 2.0, p<0.05), but no difference in plasma cortisol response.

Cost information
The authors stated that the costs of a 28-day treatment course of ciclesonide ranged from 6.66 to 47.04 euros depending on the dose, while alternative inhaled corticosteroid costs ranged from 1.29 to 33.73 euros; the numbers stem from the Department of Health Drug Tariff (May 2005). Treatment with ciclesonide would come at a substantial financial cost: a high dose (1,000 microg daily) is 5.13 times as expensive as beclomethasone, 2.27 times as expensive as budesonide (800 microg daily) and 1.39 times as expensive as fluticasone.

Authors' conclusions
The few, small, identified studies provided little evidence. The studies showed that ciclesonide has similar effectiveness and efficacy to fluticasone and budesonide, but the equivalence is not certain. There was no conclusive evidence about the effects of ciclesonide on oral deposition and hypothalamic-pituitary-adrenal suppression or side-effects compared with other inhaled corticosteroids.
CRD commentary
This was a review with a clear research question and several clear inclusion criteria, apart from a poorly defined reporting threshold (it was unclear how much and what kind of information the studies had to report to be included). The search included attempts to identify unpublished studies and no language restrictions were imposed, thereby reducing the risk of publication and language bias. Four identified abstract-only publications were excluded because there was insufficient information to assess methodological quality; these exclusions might have led to bias. According to the authors, the results from the abstracts did not alter the review's conclusion; data reported in the abstracts were based on larger samples and longer follow-up periods. The reviewers identified duplicate publications and documented the included and excluded studies in detail, allowing a clear overview of the existing evidence. Measures were taken to reduce errors and bias in the study selection and quality assessment processes, but not in the data extraction. The methodological quality of the included studies was thoroughly assessed and several factors, including the industrial funding of the included studies, were discussed.

The review considered all outcomes and the narrative synthesis was comprehensible. Overall, the conclusions appear reliable. The evidence is limited, but further data may become available when studies reported as abstracts are published in full.

Implications of the review for practice and research
Practice: The authors stated that, irrespective of any clinical benefit, ciclesonide was more expensive than other inhaled corticosteroids. It is important to highlight the limited nature of the evidence base that is currently available for scrutiny by clinicians and policy-makers seeking to practice and support evidence-based medicine. Possible advantages of ciclesonide are predicated on assertions about the long-term dangers of inhaled corticosteroids.

Research: The authors stated that further long-term trials are required to evaluate the long-term adverse effects of hypothalamic-pituitary-adrenal suppression associated with inhaled corticosteroids (including ciclesonide).

Bibliographic details
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