Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis


Authors' objectives
To examine the dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma.

Searching
MEDLINE was searched from January 1 1966 to December 1999 with the keyword 'fluticasone'. This search was combined with a search using the MeSH terms 'asthma' and 'chemical and pharmacologic phenomena' or 'dose-response relationship, drug', or the keywords 'dose' or 'dosage'. EMBASE was searched from 1980 to December 1999 using the keywords 'fluticasone' and 'dose' or 'dosage'. Additional studies were identified by contacting the manufacturer of fluticasone (GlaxoWellcome), and by examining the reference lists of all retrieved studies. Although only articles published in English were to be included, no studied reported in other languages were identified.

Study selection
Study designs of evaluations included in the review
Only double-blind, randomised placebo-controlled trials that evaluated more than one dose of inhaled fluticasone were included in the meta-analysis.

Specific interventions included in the review
All of the included studies evaluated inhaled fluticasone. The doses of fluticasone varied from 50 to 1000 µg/day.

Participants included in the review
To be included in the meta-analysis, studies had to include adolescents (aged at least 12 years) or adults with asthma. The participants had a mean age of 33 years (range: 12 to 87). In most studies the patients had moderate or severe asthma, with a mean forced expiratory volume in 1 second (FEV1) of 66% (range: 45 to 90) of that predicted at enrolment.

Outcomes assessed in the review
The outcome measures assessed were FEV1 (measured at the clinic), peak expiratory flow (PEF; both morning and evening), use of beta-agonists, night awakening, and exacerbations or withdrawal rate.

How were decisions on the relevance of primary studies made?
When making decisions on whether studies should be included in the review, two people examined the title and abstract of each paper, and the full paper if necessary.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on the following: the author(s); the number of patients; the study duration; the dose of fluticasone; the drug delivery device; the mean FEV1 and range, as a percentage of the predicted FEV1; the mean age and range; the baseline inhaled corticosteroid usage; and the outcomes.

Methods of synthesis
How were the studies combined?
For each outcome measure, the mean change reported in each study was plotted against the total daily dose of fluticasone. The authors then modelled a negative exponential curve of the mean relative percentage change from baseline for each outcome measure, weighted by the number of participants in the study. The graph was then used to determine the doses which would achieve 80 and 90% of the effect obtained with 1000 microg/day.

The authors used a meta-regression to compare the effect of a change in fluticasone dose on the asthma response variables. The odds ratios (ORs) were pooled according to whether patients taking 200 microg/day fluticasone, compared with patients taking higher doses, remained in a particular study.

A meta-analysis was conducted of the difference in effect on FEV1 of an inhaled dose of 200 microg/day of fluticasone, compared with higher doses. This was based on the standardised difference in FEV1 for the four studies from which data could be extracted.

How were differences between studies investigated?
The results indicated that heterogeneity was assessed statistically, although details of the test used were not provided in the paper.

Results of the review
Eight studies (n=2,301) met the criteria for inclusion in the meta-analysis.

Effect of dose on the mean change in outcome measure.

The raw data for each outcome measure was plotted against the dose of fluticasone. The graph showed the response beginning to plateau at a dose of 100 to 200 microg/day, with little improvement at higher doses.

Doses necessary to achieve 80 and 90% of the effect obtained with 1000 microg/day. A negative exponential line of best fit, derived from the weighted means of the effect at each dose, was modelled. From this, it was calculated that 80 and 90% of the benefit obtained with 1000 microg/day fluticasone was achieved at doses of 70 to 170 microg/day and 100 to 250 microg/day, respectively, depending on the outcome measure.

Dose necessary to achieve the maximum response. For four of the outcome measures (FEV1, morning PEF, evening PEF, beta-agonist use) it was possible to determine, by quadratic regression, the dose giving the peak effect. This ranged from 560 to 660 microg/day. In addition, it was possible to estimate the mean changes in the outcome measures.

Effect of lower versus higher doses on patients remaining in trials (5 trials). The ORs of patients remaining in a trial at a total dose of inhaled fluticasone of 200 microg/day, compared with higher doses, was 0.73 (95% confidence interval, CI: 0.49, 1.08). A test for homogeneity was not significant, with a value of 6.93 (d.f.=4, P<0.14). The random-effects pooled OR was 0.70 (95% CI: 0.38, 1.3).

Effect of lower versus higher doses on FEV1.

Four studies reported data on the comparison of 200 microg/day fluticasone with higher doses. The meta-analysis of the standardised difference in FEV1 showed a difference in FEV1 of 0.13 of a standard deviation, with a CI that included zero (95% CI: -0.02, +0.29). The pooled standard deviations for these 4 studies ranged from 0.43 to 0.76. A test for homogeneity was not significant. The random-effects pooled odds ratio was 0.13 (95% CI: -0.03, +0.30).

Authors' conclusions
In adolescent and adult patients with asthma, most of the therapeutic benefit of inhaled fluticasone was achieved with a total dose of 100 to 250 microg/day. The maximum effect was achieved with a dose of approximately 500 microg/day. However, these findings were limited by the lack of data on individual patients, and by the paucity of dose-response studies that included doses of greater than 500 microg/day.
CRD commentary
This was a reasonably well-conducted review. Two database searches were supplemented by searching the drug manufacturer's database and by examining reference lists. Appropriate inclusion criteria regarding the participants, intervention and study design were applied by two reviewers. A reasonable amount of detail was available about the individual studies, and the studies appeared to be summarised appropriately. Although the validity of the included studies was not assessed or discussed, the inclusion criteria meant that only double-blind randomised controlled trials were included. The searches of MEDLINE and EMBASE identified English language publications, but even so, one cannot discount the possibility that some relevant papers may have been missed.

The method of pooling appeared to appropriate. The authors' conclusions were supported by the findings of the review.

Implications of the review for practice and research
Practice: The authors state that national and international guidelines will need to be modified so that they recommend lower doses of fluticasone for the treatment of asthma in adolescents and adults. In addition, the pragmatic approach recommended, whereby treatment is started at a higher dose then reduced one the patient's asthma is controlled, should be reconsidered. 'Of the two alternative regimes recommended in the British Thoracic Society's guidelines for when asthma is not controlled with fluticasone at a dose of 200 to 500 microg/day, adding a long acting beta-agonist is preferable to increasing fluticasone to a dose of greater than 500 microg/day'.

Research: The authors state that some of the previous studies comparing the efficacy of different inhaled corticosteroids in patients with asthma will need to be re-examined. This is because the studies compared doses that were at, and in some cases way beyond, the top of the dose-response. The authors considered this inappropriate in the light of their findings.

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