Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux: a critical review of the literature

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Authors' objectives
To review the available evidence of the effects of antireflux therapy on asthma control in asthmatics with gastrointestinal reflux.

Searching
MEDLINE was searched from 1966 to 1996 using the following keywords combined with 'asthma': 'gastro esophageal reflux', 'antacids', 'alginates', 'cimetidine', 'ranitidine', 'famotidine', 'nizatidine', 'cisapride', 'omeprazole', 'lansoprazole', 'pantoprazole', 'domperidone' and 'metoclopramide'. The search was restricted to studies published in the English language. The reference lists of these papers were also examined for additional studies.

Study selection
Study designs of evaluations included in the review
Studies on the effects of medical reflux therapy in asthma were included. The included studies were of the following designs: randomised crossover placebo-controlled; randomised, parallel, placebo-controlled; randomised, untreated control; and open. The analysis was limited to randomised placebo-controlled studies.

Specific interventions included in the review
Interventions included the following: drug therapy with cimetidine (1 or 1.2 g/day), ranitidine (300 to 450 mg/day), cisapride (0.2 mg/kg, four times daily), or omeprazole (20 to 60 mg/day); and conservative therapy with alginates. The duration of therapy ranged from 7 days to 6 months.

Participants included in the review
Paediatric and adult patients with asthma and gastroesophageal reflux or oesophageal dysfunction were included. Oesophageal dysfunction was assessed by symptoms and abnormal manometry, and/or positive acid perfusion test.

Outcomes assessed in the review
The outcomes assessed were symptomatic gastroesophageal reflux, asthma symptoms, asthma medication use, peak expiratory flow (PEF) and spirometry.

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

Assessment of study quality
The identified studies were weighted on the quality of their design and the number of patients studied. Studies were graded A, B or C using Sackett's criteria (see Other Publications of Related Interest). Group A studies are relatively large, blinded, randomised, placebo-controlled studies; group B studies are smaller, randomised, placebo-controlled studies; and group C are uncontrolled studies. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
All 12 studies were presented and grouped by study design. The analysis of the 8 placebo-controlled randomised controlled trials involved categorising the studies as showing either improvement or no improvement on the basis of specified outcomes, then summing the number of studies (number of patients) in each group.

How were differences between studies investigated?
Differences among the trials were discussed. The trials were grouped according to study quality.

Results of the review
Twelve randomised controlled trials (325 patients) were included, of which 8 (199 patients) were placebo-controlled.

It was difficult to compare the different studies due to the diversity of the study designs. Studies were conducted over a 15-year period, during which time there have been considerable changes in asthma medications, the doses and duration of therapy, and the evaluation and treatment of gastroesophageal reflux. The participants also differed among the studies. Methodological flaws included the use of open studies and untreated controls; small sample sizes; and a lack of confirmation of gastroesophageal reflux with objective testing. None of the studies were graded as quality A. Eight studies were graded B (199 patients) and 4 studies were graded C (126 patients).

The number of studies (the corresponding number of patients was reported in brackets) showing improvement and no improvement in the outcomes were, respectively, as follows.

For grade B studies:
- asthma symptoms: 3 (121) and 4 (64) studies;
- asthma medication use, 2 (103) and 4 (64) studies;
- PEF, 2 (38) and 5 (107) studies;
- spirometry, 0 (0) and 6 (174) studies.

For improved gastroesophageal reflux (4 studies; 101 patients):
- asthma symptoms, 2 (66) and 1 (20) studies;
- asthma medication use, 1 (48) and 2 (38) studies;
- PEF, 2 (38) and 2 (63) studies;
- spirometry, 0 (0) and 4 (101) studies.

For grade C studies:
- asthma symptoms: 4 (126) and 0 (0) studies;
- asthma medication use, 2 (81) and 1 (30) studies;
- PEF, 0 (0) and 1 (30) studies;
- spirometry, 1 (15) and 2 (92) studies.

For all studies (12 studies; 325 patients):
- asthma symptoms, 7 (247) and 4 (64) studies;
asthma medication use, 4 (184) and 5 (94) studies;
PEF, 2 (38) and 6 (137) studies;
spirometry, 1 (15) and 8 (266) studies.

**Authors' conclusions**
The analysis of the combined data suggested that medical antireflux therapy improves asthma symptoms, may reduce asthma medication use, but has minimal or no effect on lung function.

**CRD commentary**
Studies were scored for quality using predetermined criteria. Details of the study designs were given. The discussion considered methodological flaws and made suggestions for future research.

By limiting the literature search to English language publications listed in MEDLINE, some relevant studies may have been omitted. No details were given of the methods used to select the primary studies, score studies on quality criteria, or extract the data. More comprehensive details of the primary studies would have been welcome, such as the criteria used to define asthma and gastroesophageal reflux, the outcomes, and the size of the treatment effects, along with confidence intervals. The figures quoted were inconsistent between tables. The pooled results were calculated by summing those studies that reported improvement, then comparing the number of studies (number of patients in these studies) reporting improvement with those reporting no improvement. The size of the treatment effect was not taken into account. Pooling the results in this manner may have been inappropriate in view of the heterogeneity of results obtained from different studies. Heterogeneity among studies was not formally evaluated.

There was insufficient evidence to support the authors' conclusion.

**Implications of the review for practice and research**
The authors consider that the challenge for future investigators is to explain the paradox of the strong association between gastroesophageal reflux and asthma, and between improvement in asthma symptoms with antireflux therapy and the absence of demonstrable changes in lung function. Which asthmatics will benefit from antireflux therapy has also to be determined.

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