LEUKOTRIENE ANTAGONIST THERAPY

ANTI-LEUKOTRIENES AS ADD-ON THERAPY TO INHALED GLUCOCORTICOIDS IN PATIENTS WITH ASTHMA: SYSTEMATIC REVIEW OF CURRENT EVIDENCE

Ducharme FM. BMJ. 2002;324:1545–1551

Purpose of the Study. To examine the evidence for the efficacy and glucocorticoid-sparing effect of oral anti-leukotrienes taken daily as add-on therapy to inhaled glucocorticoids in patients with asthma.

Study Population. Systematic review of randomized, controlled trials of children and adults with asthma comparing the addition of anti-leukotrienes or placebo to inhaled glucocorticoids.

Methods. Medline, Embase, Cinahl, and Central databases up to August 2001 were used. Trials were included if they were randomized, controlled trials, if they pertained to children and adults with asthma who were taking inhaled glucocorticoids for maintenance, if they compared the addition of anti-leukotrienes or placebo daily to inhaled glucocorticoids for a minimum of 28 days, and if they documented measures of efficacy other than compliance. Primary outcome measures were number of asthma exacerbations when the intervention was compared with the same or increased dose of inhaled glucocorticoids. It also included the change from baseline dose of inhaled glucocorticoids required to maintain control when the intervention was aimed to establish the steroid-sparing effect. Secondary outcomes were changes in pulmonary function tests, symptoms, use of rescue β₂-agonists, quality of life, exacerbations requiring hospital admission, adverse effects, and withdrawals.

Results. Of 376 citations, 13 were included (12 in adult patients; 1 in children). The addition of licensed doses of anti-leukotrienes to inhaled glucocorticoids resulted in a nonsignificant reduction in the risk of exacerbations requiring systemic steroids (2 trials; relative risk: 0.61; 95% confidence interval: 0.36–1.05). No trials comparing the use of anti-leukotrienes with double the dose of inhaled glucocorticoids could be pooled. The use of anti-leukotrienes resulted in no overall group difference in the lowest achieved dose of inhaled glucocorticoids (3 trials; weighted mean difference: −44.43 µg/day, −147.87 to 59.02; random effect model) but was associated with a reduction in withdrawals owing to poor asthma control (four trials; relative risk: 0.56; 95% confidence interval: 0.35–0.89).

Conclusions. The addition of anti-leukotrienes to inhaled glucocorticoids may modestly improve asthma control compared with inhaled glucocorticoids alone but this strategy cannot be recommended as a substitute for increasing the dose of inhaled glucocorticoids. The addition of anti-leukotrienes is possibly associated with superior asthma control after tapering of glucocorticoids, but the glucocorticoid-sparing effect cannot be quantified at present.

Reviewer’s Comments. This systematic review summarizes the evidence available through August 2001 and emphasizes the shortage of relevant trials testing the role of anti-leukotrienes as add-on therapy to inhaled glucocorticoids. Although no firm conclusion can be made, the addition of anti-leukotrienes to inhaled glucocorticoids may modestly improve the control of asthma, but there is little evidence to consider their use as a substitute for increasing doses of inhaled glucocorticoids. There is also one pediatric trial showing modest benefit, and extrapolation of adult data to children remains speculative. Additional studies are needed to evaluate the true role of anti-leukotrienes as a steroid-sparing agent, and until more evidence is available, the gold standard should remain that clinicians use inhaled corticosteroids at the lowest effective dose to maintain asthma control.

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OTHER THERAPIES

THE ROLE OF ANTICHOLINERGICS IN ACUTE ASTHMA TREATMENT


Purpose of the Study. To determine the evidence in the literature of randomized, controlled trials supporting the use of anticholinergics in the treatment of acute asthma. The study was a meta-analysis of both pediatric and adult studies, but only results of the review of pediatric studies will be reported here.

Study Population. Study subjects were between the ages of 1 and 17 years, and the studies were performed in the United States and Europe between 1985 and 2000. A total of 17 pediatric studies were included in the analysis.

Methods. The question that was proposed to answer from the literature search was: “Does the addition of inhaled anticholinergic agents to standard treatment of β₂-agonist agents decrease the likelihood of hospital admission or improve pulmonary function in the course of the emergency department (ED) visit?” A literature review using MEDLINE 1966–2001, EMBASE 1980–2001, CINAHL 1982–2001, Cochrane Review, and hand-searching major journals with cross-searching of references was performed. Studies were ranked for level of evidence with highest rank given to large randomized, controlled trials or systematic reviews of randomized trials and lower ranks for cohort and case studies. Studies were analyzed for methodology and assigned a Jadad score based on quality, with scores of 3 or higher considered of good quality. Only studies performed on asthmatics in acute care settings such as EDs were included. The primary outcome assessed by the review was need for hospitalization and secondary outcomes included pulmonary function tests, clinical or physiologic results and adverse effects.

Results. A total of 4 studies (2 systematic reviews and 2 randomized, controlled trials) involving pediatric patients presenting to the ED with acute asthma who had been treated with anticholinergic agents were examined. The dose of nebulized ipatropium bromide used in these trials was usually 250 µg per dose every 20 minutes. Frequency of dosing versus β₂-agonists was not noted in the analysis. Hospital admissions were reduced by about 30% in the subjects that were treated with multiple doses of anticholinergic agents in addition to β₂-agonists. A moderate difference was noted between the groups for change in pulmonary function. There was less benefit to adding a single dose of an anticholinergic agent to the β₂-agonists treatment of children with mild to moderate acute asthma (forced expiratory volume in 1 second [FEV₁] >50%). No apparent increase in adverse events was noted.

Conclusions. The authors conclude that the addition of anticholinergic therapy to usual β₂-agonist therapy was beneficial in pediatric patients presenting with acute asthma that was more severe by reducing the need for hospitalization and by improving lung function.

Reviewer’s Comments. This metanalysis is further evidence to support the common practice in pediatric EDs of
# Anti-Leukotrienes as Add-on Therapy to Inhaled Glucocorticoids in Patients with Asthma: Systematic Review of Current Evidence

Wanda Phipatanakul

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