

# Review: Inhaled beclomethasone reduces airflow limitations, symptoms, and the need for rescue bronchodilators in chronic asthma

Adams NP, Bestall JB, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev. 2000;(4):CD002738 (latest version 9 Jun 1999).

## QUESTION

Is beclomethasone dipropionate (BDP) efficacious for treatment of chronic asthma?

## DATA SOURCES

Studies were identified by searching the Cochrane Airways Group Trial Register (to March 1999) with the terms steroid\* (with various endings), glucocorticoid,\* corticosteroid,\* beclomethasone, budesonide, fluticasone, triamcinolone, flunisolide, Becotide, Becloforte, Pulmicort, and Flixotide; hand searching the *British Journal of Clinical Research* and the *European Journal of Clinical Research*; reviewing bibliographies of relevant papers and meeting proceedings from 3 respiratory societies; and contacting authors and the U.K. headquarters of Glaxo Wellcome.

## STUDY SELECTION

Randomized trials were selected if they compared BDP delivered by mouth inhaler with placebo in patients > 2 years of age who had a clinical diagnosis of chronic asthma; a nominal daily dose of BDP was reported; and treatment duration was  $\geq 1$  week.

## DATA EXTRACTION

Data were extracted on study design, setting, inclusion and exclusion criteria, patient char-

acteristics, drug dose, delivery device, length of intervention, and outcomes. 2 authors independently assessed each study for methodologic quality by using the Cochrane approach and the Jadad score.

## MAIN RESULTS

52 trials ( $n = 3459$ ) were included in the analysis. Overall study quality was high (42 studies had Jadad scores  $\geq 3$  out of 5; 15 studies described adequate allocation concealment). Results are reported separately for patients dependent on regular oral corticosteroids (OCSs) and are pooled across doses. Patients who received BDP had improved FEV<sub>1</sub> (7 parallel RCTs primarily of adults,  $n = 411$ , weighted mean difference [WMD] 0.34 L, 95% CI 0.19 to 0.50; 3 crossover studies of adults and children,  $n = 68$ , not significant); had greater morning (4 parallel RCTs of adults,  $n = 111$ , WMD 50 L/min, CI 8 to 92) but not evening peak expiratory flow rate (PEFR); required less rescue medication (6 parallel RCTs of adults,  $n = 343$ , WMD 1.7 puffs/d, CI 0.6 to 2.6, random-effects model); and had lower daily asthma symptom scores (4 parallel RCTs of adults,  $n = 75$ , standardized mean difference 2.6, CI 0.8 to 4.3, random-effects model) than

did patients who received placebo. Groups did not differ for local oropharyngeal side effects.

Patients dependent on OCSs who received BDP had a lower mean daily prednisolone dose (3 parallel RCTs of adults,  $n = 159$ , WMD 6.2 mg/d, CI 4.3 to 8.2) than did patients who received placebo, and they were more likely to discontinue OCSs (5 parallel RCTs of primarily adults,  $n = 274$ , RR 0.40, CI 0.23 to 0.70, random-effects model). Effects of BDP on FEV<sub>1</sub>, PEFR, symptoms, and local side effects were unclear.

## CONCLUSIONS

In adults and children with chronic asthma, inhaled beclomethasone dipropionate reduces airflow limitation, need for rescue bronchodilators, and symptoms. In patients dependent on oral corticosteroids, beclomethasone reduces use of oral prednisolone.

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## COMMENTARY

The well-done meta-analysis by Adams and colleagues clearly shows that BDP improved the FEV<sub>1</sub> (by 0.34 L) and morning PEFR (by 50 L/min) and reduced the need for rescue bronchodilators in non-steroid-dependent patients. Santanello and colleagues (1) reported a threshold value of 0.23 L (10%) for FEV<sub>1</sub> and 18.8 L/min (5%) for PEFR in patients who perceived an improvement from baseline. Patients achieved not only a statistical benefit but also a clinical benefit by exceeding these threshold values; they also had lower asthma symptom scores. Inhaled BDP resulted in a lower daily dose of prednisolone (5 mg/d) and a higher likelihood of discontinuing OCSs, with no increase in side effects with prolonged use. Dysphonia, or nonspecific throat symptoms, may occur in up to 58% of patients taking inhaled corticosteroids even when used with a spacer device (2).

No evidence existed to support a dose-response effect for any efficacy outcome. This lack of a dose-response effect has been reported with all inhaled corticosteroids. Every study showed a significant difference between all doses of inhaled corticosteroids and placebo but failed to show significant differences between adjacent doses on the dose-response curve. Usually a 4-fold or greater increase in dose has been required to show significant, but often small, differences

in lung function, symptoms, or use of rescue medications (3). One reason for the flat dose-response curve is probably related to the heterogeneous study populations with marked differences in "individual" dose-response curves.

BDP has recently been reformulated to remove fluorocarbons from the metered-dose inhaler. BDP-hydrofluoroalkane reportedly shows a marked improvement in distribution and potency. The reformulation should be considered when clinicians evaluate future studies.

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## References

1. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J*. 1999;14:23-7.
2. Williamson IJ, Matusiewicz SP, Brown PH, Greening AP, Crompton GK. Frequency of voice problems and cough in patients using pressurized aerosol inhaled steroid preparations. *Eur Respir J*. 1995;8:590-2.
3. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med*. 1998;157:S1-53.