Formoterol was more effective than terbutaline when taken as needed for moderate-to-severe asthma

Tattersfield AE, Löfdahl CG, Postma DS, et al. **Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial.** Lancet. 2001 Jan 27;357:257-61.

QUESTION

In patients with moderate-to-severe asthma who use an inhaled corticosteroid but still require as-needed medication, is formoterol (a long-acting β_2-agonist) more effective than terbutaline (a short-acting β_2-agonist) when used as needed?

DESIGN

12-week randomized (allocation concealed*), blinded (patients and investigators initially),* controlled trial.

SETTING

35 centers in Greece, the Netherlands, Norway, and Sweden.

PATIENTS

362 patients who were ≥ 18 years of age (mean age 47 y, 57% women); had had asthma for ≥ 6 months; had been treated with a constant dose of an inhaled corticosteroid for ≥ 4 weeks; had an FEV_1 of ≥ 50% of the predicted value, which increased by ≥ 12% after inhalation of 1.5 mg of terbutaline; and used their relief inhaler about 3 to 8 times per day on ≥ 7 days of the 2-week run-in period. Exclusion criteria were need for ≥ 12 inhalations of rescue medication during the run-in period or serum potassium level outside of reference range. Follow-up was 85%.

INTERVENTION

Patients were allocated to inhaled formoterol, 4.5 μg (metered dose 6 μg) (n = 182), or inhaled terbutaline, 0.5 mg (n = 180), for 12 weeks. Patients were told to take the medication only when needed.

MAIN OUTCOME MEASURES

Time to first severe exacerbation. Secondary outcomes were morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication, and safety.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the formoterol group than in the terbutaline group had ≥ 1 exacerbation {P = 0.02}† (Table). The time to first exacerbation was longer in the formoterol group than in the terbutaline group (P = 0.013). Morning and evening peak expiratory flow rates increased in the formoterol group and decreased in the terbutaline group (mean difference 11 L/min, 95% CI 3 to 20 L/min for morning; 8 L/min, CI 0 to 15 L/min for evening). The reduction in number of inhalations of relief medication was higher in the formoterol group than in the terbutaline group (mean difference 0.76 inhalations/d, CI 0.33 to 1.18). Prebronchodilator FEV_1 was increased in the formoterol group relative to the terbutaline group (mean ratio 105%, CI 101% to 108%). Both treatments were well tolerated. Groups did not differ for change in symptom scores.

CONCLUSION

In patients with moderate-to-severe asthma, formoterol was more effective than terbutaline when taken as needed.

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*See Glossary.

†*P* value calculated from data in article.

Formoterol vs terbutaline for moderate-to-severe asthma‡

Outcome at 12 mo	Formoterol	Terbutaline	RRR (95% CI)	NNT (CI)
≥ 1 exacerbation	14%	24%	40% (7.6 to 62)	11 (6 to 66)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Formoterol is a long-acting, inhaled, β_2-adrenergic receptor agonist with interesting pharmacologic properties. Despite having a duration of bronchodilating activity of > 12 hours in asthmatic patients, its onset of action is similar to the shorter-acting inhaled β_2-adrenergic receptor agonists, such as terbutaline or salbutamol. In addition, the duration of the systemic pharmacologic activity of formoterol (resulting in potential side effects) is similar to the shorter-acting inhaled β_2-agonists. This characteristic allows formoterol to be used for "as-needed" treatment of symptoms.

The study by Tattersfield and colleagues compared formoterol and terbutaline used "as-needed" in a well-designed study in adult patients who had moderately severe and uncontrolled asthma. The main outcome variable, time to first severe asthma exacerbation, is an important outcome in asthma but is not often used in clinical trials.

This study showed that fewer inhalations of "as-needed" formoterol were needed and that, somewhat surprisingly, the time to the first severe exacerbation was longer in the formoterol group. This effect on exacerbations has been previously described in a similar patient population, when formoterol, taken regularly twice daily, was added to low or moderate doses of the inhaled corticosteroid budesonide (1). The current study suggests that the ability of formoterol to reduce the risk for a severe asthma exacerbation is so robust that it can be shown even when the drug is used less frequently. These results are important to clinicians treating asthma because severe asthma exacerbations are the most dangerous events that can occur in asthmatic patients, as well as being the most demanding and expensive for the health care system. This benefit of formoterol was not accompanied by an increase in β_2-agonist–related side effects. The study has convincingly shown that in addition to the already well-accepted benefits of the regular use of inhaled formoterol, "as-needed" use provides more clinical benefit to asthmatic patients than does use of the shorter-acting terbutaline.

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Reference

1. **Pauwels RA, Lofdahl CG, Postma DS, et al.** Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997;337:1405-11.

