Critical Appraisal

Is it time for single-inhaler asthma therapy?

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O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.

Research question

Would asthmatic patients receiving a low maintenance dose of budesonide-formoterol (B/F) have better asthma control if their short-acting beta$_2$-agonist reliever were replaced with as-needed B/F?

Type of article and design

Double-blind, randomized, parallel-group, 12-month study conducted at 246 centres in 22 countries.

Relevance to family physicians

Combining an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist in one inhaler represents an important advance in asthma management. Numerous studies have documented the superiority of combination therapy over higher doses of ICS alone.[1-5] In Canada, 2 dry powder combination products are available in a single inhaler: Symbicort Turbuhaler (B/F) and Advair (fluticasone-salmeterol). Onset of bronchodilator action with the Symbicort Turbuhaler occurs within the first minute.[6]

Fewer severe exacerbations of asthma are observed among patients using as-needed formoterol in addition to regular maintenance therapy with an ICS or an ICS combined with a long-acting beta$_2$-agonist than in patients using terbutaline[7] or salbutamol[8] as needed. Given the slow onset of action of salmeterol, using fluticasone-salmeterol as both maintenance and rescue therapy is not an option.

Use of a single inhaler for maintenance and rescue simplifies asthma therapy for both patients and physicians and might promote compliance. It likely reflects what happens in the real world where patients tend to take more medication in response to more severe symptoms. Use of a single inhaler ensures that patients obtain both bronchodilator (rapid) and anti-inflammatory benefits without risk of over-reliance on beta$_2$-agonist medication.

Overview of study and outcomes

This study included outpatients aged 4 to 80 years with asthma using 400 to 1000 µg/d of ICS (adults) or 200 to 500 µg/d of ICS (children 4 to 11 years old with a history of at least 1 asthma exacerbation in the preceding year). Patients had a forced expiratory volume in 1 second between 60% and 100% of predicted with 12% reversibility.

Patients were randomly assigned to 1 of 3 treatment arms: 80/4.5 µg of B/F twice daily plus 80/4.5 µg of B/F as needed (B/F/N), 80/4.5 µg of B/F twice daily plus 0.4 mg of terbutaline as needed (B/F/T), or 320 µg of budesonide twice daily plus 0.4 mg of terbutaline as needed (B/T). Children received half the maintenance dose once daily at night. Treatment stratification was by age group in an 8:1 ratio (adults:children). All medication was delivered by Turbuhaler.

Time to first exacerbation of asthma was chosen as the primary end point and was defined as a deterioration in asthma control resulting in hospitalization or emergency room treatment, oral steroid treatment (or an increase in ICS via separate inhaler or other additional treatment for children), or morning peak expiratory flow of 70% or less of baseline on 2 consecutive days. Severe exacerbations were treated with a 10-day course of oral prednisone (30 mg/d). For children, additional maintenance could also be used. The sample size was based on the true incidence of asthma exacerbation in one group being 25%. The study had the power to provide an 80% probability of detecting a reduction of more than 23% of exacerbations in another group.

Results

The B/F/N strategy significantly prolonged time to first severe exacerbation when compared with B/F/T and B/T (both $P<.001$). In the B/F/N group, 11% of patients experienced severe exacerbations requiring medical intervention compared with 19% and 21% in the B/T and B/F/T groups, respectively ($P<.001$ for B/F/N vs B/T and B/F/T). Average daily dose of budesonide in the B/F/N arm was 80 µg higher than in the B/F/T arm and less than half the dose of ICS taken in the B/T arm.

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Analysis of methodology

This asthma study is the first to evaluate the efficacy of a combination inhaler (B/F/N) for children, adolescents, and adults for both maintenance and rescue therapy and compare it with the same fixed maintenance dose (B/F/T) and with a 4 times greater dose of budesonide alone (B/T), both using terbutaline as rescue therapy.

The selection of patients with moderate-to-severe disease might limit how the results of this study can be generalized to patients with mild asthma. An important strength of this study is a design that allows evaluation of how strategic use of medication compares with fixed dosing in terms of both asthma outcomes and total medication used.

Application to clinical practice

This study demonstrates superior asthma control using combination therapy (B/F) in a single inhaler both for maintenance and rescue compared with fixed-dose therapy using a minimum of 2 inhalers (B/F/T and B/T). The benefits achieved in both children and adults using B/F/N (compared with a 4 times higher dose of budesonide [B/T]) suggest that it is the timing of the increase in ICS (resulting from as-needed use of B/F) rather than the total inhaled dose of ICS that confers the benefit. Using this strategy with combination therapy is consistent with current guidelines[9] that advocate achieving and maintaining control of asthma using the lowest effective dose of medication.

While this strategy is well suited to address asthma's variable course over time, more studies are needed among patients with less severe disease to fully understand its potential role in the real world.

Bottom line

- Single-inhaler combination therapy (B/F/N) for both maintenance and rescue provides superior asthma control compared with B/F/T and B/T therapy for children and adults.
- The strategic increase in ICS, rather than the total amount of ICS, confers superior asthma control.
- Similar studies are needed among patients with less severe disease.
- Further studies are needed to clarify how each of the medication components in the B/F/N arm contributed to improved asthma control.
- Single-inhaler asthma therapy represents a unique and important advance that could simplify asthma management for both patients and physicians.

Competing interests

This study was funded by AstraZeneca R&D in Lund, Sweden. No funding was provided for preparation of this article, however, or for presenting study data in any forum.

Points saillants

- La thérapie combinée à inhalateur unique (B/F/au besoin) pour la prise en charge continue et en cas de besoin permet un contrôle supérieur par rapport à la thérapie aux B/F/T et aux B/T pour les enfants et les adultes.
- L'augmentation stratégique dans les corticostéroïdes inhalés (CSI), plutôt que le montant total de CSI, permet un contrôle supérieur de l'asthme.
- Il faut réaliser des études semblables auprès des patients chez qui la maladie est moins grave.
- D'autres études sont nécessaires pour déterminer comment chaque composante du médicament dans la combinaison aux B/F/au besoin a contribué à l'amélioration du contrôle de l'asthme.
- Le traitement de l'asthme à l'aide d'un inhalateur unique représente un progrès inédit et important qui pourrait simplifier la prise en charge de l'asthme, tant pour les patients que pour les médecins.

References

1. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing ICS. *Lancet* 1994;344:219-24.
2. Woolclock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroid with doubling of the dose of inhaled steroid. *Am J Respir Crit Care Med* 1996;153:1481-8.
3. Pauwels RA, Lafdahl CG, Postma DS, Tattersfield AE, O'Byrne PM, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11.
4. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistant asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1392-7.
5. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels R, et al. Can guideline-defined asthma control be achieved? The gaining Optimal Asthma Control Study. *Am J Respir Crit Care Med* 2004;170:836-44.
6. Van der Woude HJ, Borsman M, Bergqvist PB, Winter TH, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. *Pulm Pharmacol Ther* 2004;17:89-95.
7. Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparision of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.
8. Pauwels RA, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, et al. Formoterol as relief medication in asthma: a worldwide effectiveness trial. *Eur Respir J* 2003;22:787-94.
9. Lemiere C, Bai T, Balter M, Bayliff C, Becker A, Boulet LP, et al. Adult Asthma Consensus Guidelines Update 2003. *Can Respir J* 2004;11(Suppl A):9A-18A.

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