

Options for bronchodilation in children: can we rely on adult data?

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Bronchodilators, especially β_2 -agonists, are effective in relieving asthma symptoms. Therefore, short-acting β_2 -agonists are recommended in all guidelines on a p.r.n. basis, usually in combination with anti-inflammatory treatment, at least in moderate to severe asthma. Although for adult asthma some concerns have been raised about regular use of short-acting β_2 -agonists, studies in children do not suggest that continuous use results in deterioration of asthma. This question is more relevant to the chronic use of the long-acting β_2 -agonists, salmeterol and formoterol. These drugs may be used instead of anti-inflammatory drugs, especially inhaled corticosteroids. Recent studies in adult asthmatics have supported the use of a long-acting β_2 -agonist in combination with a lower dose of inhaled corticosteroid in preference to a higher dose of inhaled corticosteroid. So far, data in children are less convincing for this therapeutic strategy. It may be that differences in the disease process between adults and children are likely to account for these different responses in treatment regimens. Furthermore, it has to be determined whether treatment should primarily aim at symptom reduction or whether other disease parameters should also be taken into account.

The title, "Options for bronchodilation in children", can be explained in two different ways. In the first place, it could be read as strategies to reach the optimal airway caliber. Secondly, in a more strict sense, several classes of bronchodilators which are used in the treatment of childhood asthma could be discussed. Regarding the first explanation, international consensus reports for adults as well as children recommend the use of inhaled corticosteroids to achieve optimal symptom control as well as optimal lung function, e.g., maximal airway caliber, at least in moderate and severe asthma (1, 2). According to these consensus reports, short-acting β_2 -agonists should be used

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on a p.r.n. basis to relieve symptoms. This also leads to the second interpretation of the title. Although other classes of bronchodilators such as anticholinergics and theophyllines are on the market, short-acting β_2 -agonists have a prominent place in the consensus reports as effective drugs to achieve bronchodilation and offset the bronchoconstrictive effectors which cause symptoms. More recently, long-acting β_2 -agonists, such as formoterol and salmeterol, have become available, and now are beginning to gain a place in the treatment plan.

Short-acting β_2 -agonists

After inhalation of short-acting β_2 -agonists, a rapid onset of bronchodilation occurs, which is felt as symptomatic relief for patients (3). This immediate effect may lead to over-reliance on these drugs and result in chronic regular use. However, β_2 -agonists, in contrast to inhaled corticosteroids, do not influence the inflammatory process in asthmatic airways (4). Epidemiologic data from adult studies in New Zealand and Canada in the past decade, suggesting a correlation between the use of β_2 -agonists and asthma deaths, have started a discussion of the negative effects of these drugs (5–7). However, this correlation may be explained by confounding with severity of the disease. Because in childhood the asthma mortality rate is extremely low, the clinical relevance is even less clear (8). Although in adults two studies revealed a deterioration of asthma during continuous use of short-acting β_2 -agonists (9, 10), this has not been confirmed in children during treatment for more than 2 years (11). Another negative effect contributing to regular use of β_2 -agonists is the rebound effect after stopping treatment (12). However, the clinical relevance of this phenomenon is not clear and has not been studied in children. Despite the negative publications on this class of drugs, they now have an established place as drugs for symptom relief on a p.r.n. basis in all severity grades of asthma (12).

Anticholinergics

The potency of inhaled ipratropium bromide in terms of bronchodilation is less than that of β_2 -agonists; therefore, these drugs are not considered first-line bronchodilators in the treatment of asthma (13). During acute exacerbations, ipratropium may have an additional effect (14).

Theophylline

Theophylline has been widely used as a bronchodilator also in children, especially when inhalation of β_2 -agonists in this age group is troublesome or impossible. The availability of small-volume spacers in combination with β_2 -agonists for younger children and the frequent side-effects of theophylline at doses necessary to obtain an adequate bronchodilating effect (15) ruled out this drug as a first-line bronchodilator in childhood asthma. More recently, it has been suggested that theophylline even at lower plasma concentrations has immunomodulating and anti-inflammatory effects (16). Further clinical studies are necessary in order to evaluate the relevance of this.

Long-acting β_2 -agonists

Two inhaled, long-acting β_2 -agonists, formoterol and salmeterol, are available now. After inhalation of a single dose, they gave prolonged bronchodilation and protection against various bronchoconstricting stimuli such as methacholine, histamine, exercise, hyperventilation with dry cold air, and allergen (17). Used twice daily for several weeks or months, these drugs result in better symptom control and higher peak flows than placebo or salbutamol in studies in adults and children (18–20). Compared to increasing (doubling) the dose of an inhaled corticosteroid, the addition of salmeterol resulted in fewer symptoms and better peak flows in adults with moderate and severe asthma (21, 22). These studies did not show a difference in exacerbation rates between the two therapeutic regimens. A recent large multicenter study in adult asthmatics showed that the addition of formoterol resulted in fewer mild and severe exacerbations for groups treated with low and high doses of budesonide (23). Mild exacerbations were as effectively prevented by a low dose of budesonide plus formoterol as by a high dose of budesonide; however, a high dose of budesonide was superior to a low dose in combination with formoterol in suppressing severe exacerbations. Mild exacerbations were defined as increased use of rescue bronchodilator and/or mild lowering of peak flow and/or awakenings at night, while severe exacerbations were those in which there was at least a moderate decrease in peak flow and/or dosage of oral corticosteroid.

These studies suggest that addition of a long-acting β_2 -agonist in adult asthma may be more effective than increasing the dose of inhaled corticosteroid for suppressing asthma symptoms, whereas there are no data to suggest a deterioration of asthma during this regular treatment. The

use of long-acting β_2 -agonists instead of inhaled corticosteroids may be of particular interest in children, for in this group the risk of side-effects of inhaled corticosteroids, especially on growth and bone density, is greater than in adults. However, it has to be kept in mind that these drugs, which are effective bronchodilators, have so far not expressed anti-inflammatory effects in clinical studies and therefore are unlikely to influence the progression of the disease (24). Two studies in asthmatic children have compared the effect of monotherapy with salmeterol with a moderate dose of beclomethasone (25, 26). Except for growth, beclomethasone therapy was superior in all clinical effect parameters during the 1-year treatment period.

More clinically relevant may be the question of whether the addition of a long-acting β_2 -agonist to a low or moderate dose of inhaled corticosteroid is more effective than doubling the dose of inhaled corticosteroid. This question was addressed in a three-arm parallel study in 177 children comparing 400 μg beclomethasone daily with the same dose plus salmeterol and with 800 μg beclomethasone (27). This study, however, did not show any significant differences between treatment groups in symptom scores, peak flows, FEV₁, or airway responsiveness after the 1-year treatment period. Due to the extremely high compliance with medication, all groups significantly improved, including the group treated with 400 μg beclomethasone, which was comparable with treatment before entering the study. These results are somewhat in contrast with the more favorable results of adding long-acting β_2 -agonists in the previously mentioned adult studies (21–23).

Although differences in outcomes may be due to different selection criteria before entrance to the study, it is unlikely that this is the sole explanation. It may be hypothesized that differences in the disease state between adults and children favor the effects of inhaled corticosteroids in children. A relatively short-standing inflammatory process in childhood asthma could be rendered more reversible or suppressible by inhaled corticosteroids, whereas, in adults with usually

long-standing disease, airway remodeling may have occurred which is less susceptible to inhaled corticosteroids (28). There is indirect evidence that early introduction of inhaled corticosteroids results in better therapeutic responses (29, 30). Theoretically, due to the effect of an inhaled corticosteroid in children, few or even no residual bronchoconstriction may remain, a fact which therefore limits the effect of a long-acting β_2 -agonist. Because in the study in children (27) no differences between 400 and 800 μg beclomethasone daily could be found in clinical effect parameters in this group of children with moderate asthma and excellent compliance with medication, it may be worthwhile to investigate the additional effects of a long-acting β_2 -agonist on lower doses of inhaled corticosteroids. This is even more relevant, for both doses of inhaled corticosteroid in this study were shown to have a small, but significant effect on growth.

Conclusions

Inhaled corticosteroids remain the cornerstone of asthma treatment in children with at least moderate to severe asthma (2). Short-acting β_2 -agonists are necessary for relief of symptoms in all children with asthma on a p.r.n. basis. Long-acting β_2 -agonists should be used only in combination with an inhaled corticosteroid, and their use may be considered instead of further increasing the dose of an inhaled corticosteroid. So far, no clinical characteristics have been identified to determine whether the addition of a long-acting β_2 -agonist or an increase in inhaled corticosteroid will affect the course of the disease for an individual patient. Further developments of airway inflammation markers and clinical validation of these markers may provide new options in future asthma management.

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