

Choices of therapy for exercise-induced asthma in children

Cough and wheezing interferes with sport and other forms of physical activity in half of asthmatic children. Airway obstruction can be induced by a standard exercise test in over 70% of children with asthma. A beta-adrenergic agonist or cromone taken by inhalation beforehand will usually inhibit bronchoconstriction provoked by a free running exercise test. The duration of protective effect with salbutamol, terbutaline and cromones is less than 4 h. The long acting beta-adrenergic agonists formoterol and salmeterol give protection against exercise-induced airway obstruction for up to 12 h, which implies that treatment given in the morning will offer protection from the effects of physical activity throughout the day. However, the duration of protective effect after a morning dose declines if these compounds are given regularly. Leukotriene receptor antagonists (LRAs) also provide good protection against exercise-induced asthma. Regular administration of LRAs is not associated with tolerance and loss of protective effect. The oral route makes for unobtrusive administration and this may help adherence to prescribed regimens.

John F. Price

Variety Club Children's Hospital, King's College
Hospital, London, UK

Professor John F. Price
Variety Club Children's Hospital
King's College Hospital
London SE5 9 RS
UK

If from running, gymnastic exercise, or any other work, the breathing become difficult it is called asthma; and the disease Orthopnoea is also called asthma, for in the paroxysms the patients also pant for breath...
Aetæus the Cappadocian (1)

The size of the problem

Despite awareness for many centuries that exercise can provoke attacks of asthma, the mechanism is still not fully understood. A widely accepted explanation is that heat and water loss from the surface of the respiratory tract during exercise leads to hyper-osmolar stimulation of mast cells which degranulate and release mediators of bronchoconstriction. Compounds which stabilize mast cells or which antagonize the mediators they release have the potential to prevent exercise-induced asthma.

Perhaps the strongest impact asthma can have on a child's wellbeing and ability to mix with their peers is through restriction of daily activity. Two large UK surveys have documented prevalence rates of exercise related symptoms in 87% (2) and 80% (3) of asthmatic children. One of these surveys found that more than 50% of children were at times unable to complete a sports lesson because of asthma. Sports that involve outdoor running were those most affected. Nevertheless, 11% of children found swimming provoked symptoms, a sport generally considered to be well tolerated by asthma sufferers. Many children also found that social play and other outdoor activities such as camping, horse-riding and walking in the country were curtailed by their asthma.

Activity is an important trigger of asthma at all stages of childhood. Structured interviews with preschool children and their parents who were attending a hospital-based asthma clinic found that physical activity caused wheezing in 88% of the children (4). Impairment of activity is also a problem in older children with asthma. This was assessed in students aged 13–14 years attending 32 Australian secondary schools. A quality of life questionnaire (QOL) was used which included questions about activity. Asthma limited the activities of 35% of students during the previous 2 weeks, most commonly affecting outdoor sports, running up hills, cycling and swimming (5).

Many asthma-provoking physical activities take place at school. However, studies in the UK (6) and Australia (5) have shown that schoolteachers are not well informed about exercise-induced asthma and its management. Although three-quarters of secondary school teachers were able to name a beta-agonist as useful treatment during an asthma attack, only 6% were able to give the correct answer when asked about prevention of exercise induced asthma (5). In many schools children are not encouraged to keep their inhalers with them so, inevitably management of exercise-induced asthma (EIA) is not ideal.

Methods of evaluation

Free running exercise test

The response to exercise can be assessed by free running, running on a treadmill, or exercise bicycle.

Standard protocols are available for each method but the most widely used is treadmill running. Airway obstruction can be induced by a standard exercise test in over 70% of children with asthma (7). The degree of bronchoconstriction is affected by relative humidity and temperature of the inspired air and this should be regulated. The exercise lasts for 6–10 min and needs to cause an increase in heart rate to 75% of the maximum for age. Although bronchoconstriction can occur during exercise, it is quite common to see a small amount of bronchodilatation. Characteristically, maximum bronchoconstriction occurs about 5 min after the end of the exercise period. Lung function, usually FEV_1 , should be measured frequently until lung function returns to baseline. There are three main endpoints which have been used to describe the airway obstruction which follows a standard free running exercise test and to assess the protective effect of treatment (Fig. 1):

- 1) *Maximum fall in FEV_1 .* Maximum bronchoconstriction and therefore maximum fall in FEV_1 from pre-exercise baseline is expressed as the percentage change and usually occurs 5–10 min after the period of exercise.
- 2) *Time to recovery.* Lung function takes anything from 15 min to an hour to return to baseline. Time to recovery is normally expressed as the time taken for the FEV_1 to return from maximum fall to within 5% of the pre-exercise baseline value.
- 3) *"Area above the curve".* This is calculated using the series of FEV_1 measurements made after exercise. The area above a curve generated by serial recordings of percentage fall from pre-exercise FEV_1 during the course of 1 h after completion of the exercise challenge (AAC 0–60 min) represents the combined impact of maximum fall and time to recovery. This can be calculated using the trapezoidal method.

Strenuous exercise or a standard exercise test is followed by a refractory period during which the bronchoconstrictor response to exercise is attenuated. This is seen in about 60% of people with exercise-induced asthma (8) and lasts for up to 2 h. Exercise tests performed on the same day 2 h or more apart are very reproducible and can be used to test the duration of protective effect of a single dose of treatment.

Diary cards and Quality of Life questionnaires

Lung function tests such as FEV_1 provide an objective assessment of airways obstruction but do not measure how a patient feels. Outcome measures that reflect the child's and parents' perceptions, although subjective, may give a more comprehensive assessment of the impact of the illness on daily life. Two methods have been used and both include an evaluation of the effect

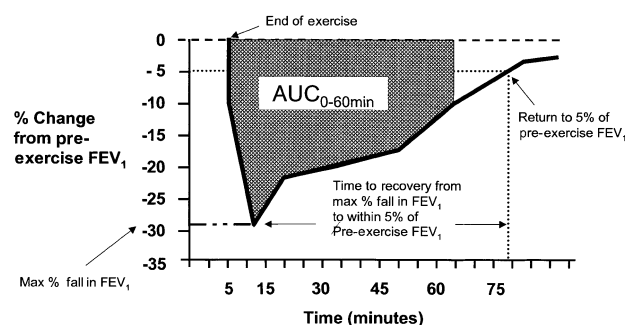


Figure 1. Endpoints used to describe the response to exercise and assess the effect of treatment in children with exercise-induced asthma: (a) maximum fall in FEV_1 ; (b) time to recovery; (c) area above the curve.

of asthma on physical activity; the first is a daily record of symptoms on diary cards and the second is an asthma specific quality of life questionnaire.

A diary card on which impairment of activity is recorded is often used to assess severity in clinical practice and to assess change in clinical trials. Relatively little work has been carried out to validate such records of activity limitation in childhood asthma. Daytime symptom and activity questions completed by children with asthma aged 6–14 years correlates moderately with changes in morning and evening peak flow and with evening doses of bronchodilator, but not with changes in percentage predicted FEV_1 (9).

A self-administered QOL questionnaire has been specifically developed and validated for children with asthma of 9 years of age and older. One of the three domains comprises five questions related to asthma and activity. Each answer uses a seven-point scale ranging from worst to best. Although QOL questionnaires were originally developed and validated for surveys; this questionnaire has been used successfully to measure change in clinical trials (10). Asthma-specific QOL questionnaires are being developed for use in younger children but have the potential disadvantage that they can not be self-administered.

Choices of treatment

Studies carried out 25 years ago, when techniques for exercise testing in children with asthma were being standardized, showed that several different compounds if given before free running exercise reduced the fall in lung function which followed. These early studies indicated that the most effective compound was the short-acting beta-agonist salbutamol, followed by sodium cromoglycate (11). Oral theophylline also conferred some protection. The degree of inhibition of exercise-induced bronchoconstriction (EIB) with theophylline appeared to correlate with serum concentration of the drug (12, 13). Atropine-like compounds are relatively ineffective in blocking EIB. Regular

treatment with inhaled steroids for 1–2 months attenuates airway obstruction following exercise. In the case of budesonide the protective effect shows a dose dependent relationship over the dose range 100–400 mcg per day, giving about 80% protection at the higher dose (14). Some data indicated that the protective effect of inhaled steroids may decrease over time (15). Cysteinyl leukotriene release has been implicated in the mechanism of exercise-induced asthma, and not surprisingly the newly developed leukotriene receptor antagonists have an inhibitory effect on EIB.

Beta-adrenergic agonists

The short acting beta-adrenergic agonists salbutamol and terbutaline are potent inhibitors of EIB. However, the duration of protective effect is quite short. Repeated exercise testing at 2-hourly intervals after a single dose showed that in one-third of children the protective effect had worn off after 2 h and in less than a half did it persist for more than 4 h (16). The value of short-acting beta-agonists to treat EIB in schoolchildren is limited by current regulations which prevent children carrying their own inhalers and lack of knowledge among teachers about how to prevent EIB. Children are active throughout the day and it is impractical to keep giving treatment before every period of physical exercise.

Salmeterol and formoterol have a longer duration of bronchodilation and afford more prolonged protection against EIB. A placebo-controlled trial in children demonstrated greater than 90% inhibition of EIB, expressed as the maximum fall in FEV₁, 1, 5 and 9 hours after a single dose of 50 mcg salmeterol (17). This prolonged protection was achieved with low inspiratory flow (30 l/min) from a dry powder breath-actuated inhaler (18). Some protection was seen at 12 h and this appeared to be dose-dependent. Both 25 mcg and 50 mcg of salmeterol given to children aged 7–14 years almost completely inhibited EIB 1 h after exercise, but 50 mcg afforded better protection after 12 h. The higher dose gave about 50% protection at 12 h (19). Formoterol has a more rapid onset of bronchodilation than salmeterol. One study in children has demonstrated almost complete inhibition of EIB at 3 h and greater than 60% inhibition of EIB at 12 h following pretreatment with formoterol 12 mcg (20). The degree of protective effect has varied in different studies but all studies have confirmed the long duration of inhibition of EIB in children with both salmeterol and formoterol. These single-dose studies suggest that a long-acting beta-agonist given in the morning will offer some protection throughout the day against symptoms provoked by sport and other physical activity.

The bronchodilator effects of beta-adrenergic agonists may be age-dependent. Using cumulative inhaled doses Turner and colleagues defined dose–response

curves for bronchodilation with salbutamol in children over the age range 3–9 years. The results suggest that bronchodilator responses to salbutamol increase with age in young children with asthma (Fig. 2) (21). In adult patients with poor asthma control despite treatment with an inhaled steroid, the addition of a long-acting beta-agonist confers greater benefit than doubling the dose of the inhaled steroid (22). However, a study of similar design in children did not show the same superiority for the long-acting beta-agonist compared with increasing the inhaled steroid (23). The relationship between age and degree of inhibition of EIB by short- or long-acting beta agonists has not been investigated fully.

With regular administration the duration of inhibition of EIB by a long-acting beta-agonist declines. In a randomized, double-blind cross-over study salmeterol 50 mcg was given once daily to young adolescents aged 12–16 years with asthma. Treatment was for 28 days and compliance was monitored using cronolog inhaler devices. Exercise challenge tests were performed 1 and 9 h after salmeterol or placebo on the 1st and 28th day of each treatment period. On the first day of treatment there was effective inhibition of EIB with salmeterol at 1 and 9 h. On the 28th day of treatment the protective effect of salmeterol at 1 h was undiminished, but the protective effect at 9 h was lost (Fig. 3). All the patients were taking beclomethasone throughout the study, so concomitant treatment with an inhaled steroid did not prevent the development of tolerance (24).

Cromones

The protective effect of di-sodium cromoglycate (DSCG) against exercise-induced airway obstruction was demonstrated first in the early 1970s (25). Both DSCG and nedocromil sodium have been shown to

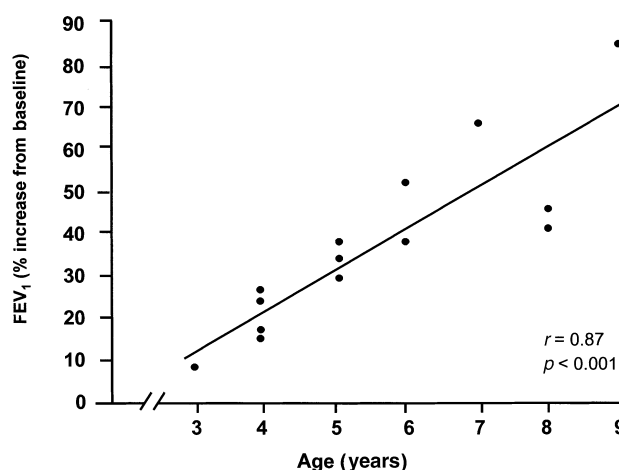


Figure 2. The increase in FEV₁ (%) after inhaling a cumulative nebulized dose of salbutamol of 6.84 mg in 14 children with asthma aged 3–9. Individual data points and the regression line are shown. Adapted from Turner et al. (21).

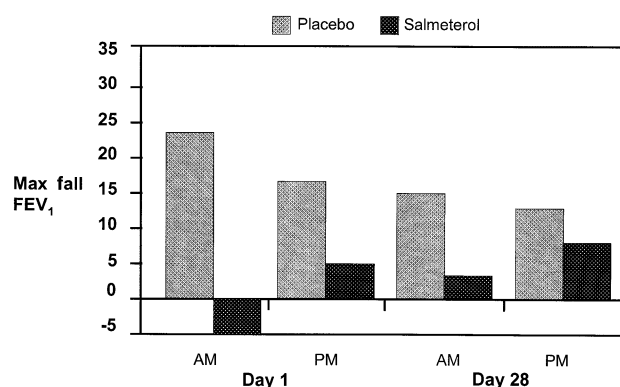


Figure 3. Mean ($\pm$ SD) maximum fall in FEV₁ after exercise 1 and 9 h after giving salmeterol 50 mcg or placebo in 14 subjects aged 12–18 years. After 28 days of continuous salmeterol 50 mcg daily, the mean maximum fall in FEV₁ after exercise at the 9-h time-point did not differ significantly from placebo.

reduce exercise-induced bronchoconstriction by more than 50% (26). It has been suggested that nedocromil sodium has a greater protective effect than DSCG (27). However, in children DSCG 10 mg and nedocromil sodium 4 mg gave equal protection against exercise-induced asthma 20 min after administration. The duration of protection with both compounds lasted less than 2 h (28). When DSCG is combined with terbutaline the protective effect is extended to 4 h but lost by 6 h (29). Nedocromil sodium has an unpleasant taste and DSCG may cause coughing immediately after inhalation.

Both short-acting beta-agonists and DSCG reduce the energy cost of running in children with exercise-induced asthma. In a placebo-controlled trial oxygen uptake was reduced during exercise when asthmatic children inhaled salbutamol or DSCG beforehand (30). This effect of beta-agonists and DSCG is also seen in asthmatic children without EIB but not in healthy children (31). There are few comparisons of the protective effect of short-acting beta-agonist and cromones but one carried out in the mid-1970s suggested that greater inhibition was achieved with salbutamol than with DSCG (14). Because beta-agonists are bronchodilators as well as protecting against EIB it has been proposed they should be used before exercise in children with pre-existing airway obstruction. The use of cromones may be more appropriate in children with vulnerability to EIB but no airway obstruction before exercise (32).

Leukotriene receptor antagonists

The cysteine-containing leukotrienes, LTC₄, LTD₄ and the less potent but more stable metabolite LTE₄ are synthesized from arachidonic acid through the 5-lipoxygenase pathway. They are potent mediators of bronchoconstriction, stimulate mucous secretion and increase vascular permeability. The cysteinyl leukotrienes are

released from a range of inflammatory cells, notably mast cells and eosinophils, and have been implicated in the pathogenesis of exercise-induced airway obstruction. Levels of urinary LTE₄ are elevated in asthmatic children both during and between attacks (33). An increase in urinary LTE₄ has been observed after exercise in adults and in children with severe asthma (34), although neither the pre-exercise LTE₄ nor the rise in LTE₄ after exercise correlated with the degree of exercise-induced bronchoconstriction (35). Leukotriene receptor antagonists (LRAs) taken regularly improve asthma symptoms and lung function in adults and children. In adults they block both early and late reactions to antigen challenge and reduce sputum eosinophilia (36). In asthmatic children they reduce NO in exhaled air (37). Their value in treating asthmatic children with symptoms provoked by physical activity has been assessed by exercise challenge and quality of life questionnaire.

Montelukast is an orally active LTD₄ receptor antagonist. The effect of 5 mg administered once daily on exercise challenge was assessed in 27 children aged 6–14 years with stable asthma. The study was randomized double-blind placebo-controlled cross-over in design. Six-minute treadmill exercise challenges were performed 20–24 h after the last dose in each trial period. Montelukast significantly reduced the AAC_{0–60min} (59% inhibition relative to placebo; $P \leq 0.05$), the maximum % fall in FEV₁ (31% inhibition relative to placebo; $P \leq 0.05$), but not the time to recovery (mean reduction 10 min) (Fig. 4). There was no correlation between age and the degree of inhibition of EIB and no suggestion that younger children were less well protected (38). Although Montelukast did not completely prevent EIB, the results of this study suggest that a single oral dose given in the evening will confer a considerable degree of protection throughout the following day.

A further study examined the impact of montelukast on activity induced symptoms through the use of a quality of life questionnaire. The questionnaire was one

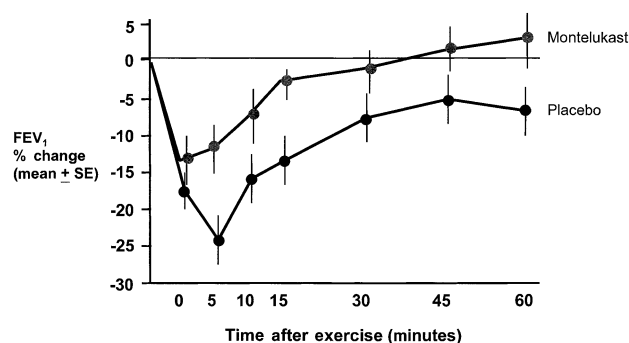


Figure 4. The mean change in FEV₁ (%) after exercise from pre-exercise baseline in 25 children aged 6–14 years. The area over the FEV₁ time curve for 0–60 min after exercise (AAC_{0–60 min}) was reduced by 60% after treatment with montelukast compared with placebo.

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of the secondary variables in a randomized double-blind controlled trial comparing montelukast with placebo in children with either intermittent or persistent asthma. Children in the study aged 9–14 years completed a self-administered paediatric asthma specific quality of life questionnaire (13) before starting treatment and at the end of the 8-week treatment period. The questionnaire included an “activity domain” containing five questions, which related to the impact of asthma on physical exercise activity. Answers were rated on a seven-point scale (1 = worst, 7 = best). Average scores before treatment were around 4.5. They improved by a mean of 1.1 for montelukast compared with 0.6 for placebo ($P < 0.001$) (39).

No controlled studies have been published to describe the impact of long-term treatment with LRAs on EIB in asthmatic children. However, studies in adults suggest that tolerance and loss of protective effect do not occur. The degree of inhibition of EIB was undiminished in asthma patients aged 15–45 years after 4, 8 and 12 weeks' continuous treatment with montelukast 10 mg daily. Two weeks after cessation of treatment the exercise response had returned to baseline (40). In adults but not in children montelukast has been compared with salmeterol for the capacity to give sustained protection against EIB. When treatment was initiated the compounds gave equivalent protection, but greater

protection was seen with the LRA after 4 and 8 weeks. This was due to a decline in the protection afforded by salmeterol over time (41).

The oral route provides unobtrusive administration and this may help adherence to prescribed regimens. A preliminary report of a study involving nearly 300 families not surprisingly indicated that oral montelukast taken once daily was preferred by most children and their parents, and compliance was better when compared with inhaled cromolyn by metered-dose inhaler prescribed four times daily (42).

Conclusions

Activity-induced symptoms are common in asthmatic children and interfere with quality of life. Short-acting beta-adrenergic agonists produce rapid bronchodilation and effective protection against EIB for 2–4 h. Pretreatment with cromones may have a place in children with EIB who, at most other times, have normal lung function. Long-acting beta-agonists provide protection against exercise induced asthma for up to 12 h. Leukotriene receptor antagonists administered once daily give effective protection against activity induced symptoms throughout the 24 h and there is no evidence that their effect wanes when they are taken regularly.

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