EDITORIAL

Drugs and the control of exercise-induced asthma

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Exercise-induced asthma (EIA) is the name used to describe the transitory increase in airways resistance which follows vigorous exercise in most patients with asthma [1]. EIA has been recognized since ancient times, but the first modern clinical description was given by Jones et al. [2] of Liverpool, UK in 1962.

Exercise is acknowledged by many paediatricians to be the most common cause for an attack of asthma in child-ren, and the presence of EIA is diagnostic of asthma. Using standardized protocols for exercise challenge, EIA can be demonstrated in the laboratory in 70–80% of clinically recognized asthmatic adults and children. In the general population, the prevalence of EIA is reported to be 4–12%, and an increase in prevalence from 6.7 to 7.7% was reported in the UK between 1973 and 1988 [1].

A reduction of 10% or more in forced expiratory volume in one second (FEV1) or peak expiratory flow rate (PEFR) in the laboratory is diagnostic of EIA. Like other attacks of asthma, EIA is accompanied by a reduction in arterial oxygen tension and lung hyperinflation. Fifty percent of subjects are refractory to the effects of exercise, when it is repeated within 30–90 min. There is no increase in bronchial responsiveness to other stimuli following exercise, and the airway response is usually reproducible when the challenge is repeated after an interval of 3–4 h [1].

The stimulus to EIA is the evaporative water loss, which occurs in the airways when conditioning large volumes of air to alveolar temperature and water content in a short time. The mechanism whereby water loss causes the airways to narrow is thought to be due to its thermal and dehydrating effects, which produce a hyperosmolarity of the airways. This is accompanied by the release of mast cell mediators and possibly neural stimulation, which, in turn, cause the airways to narrow by contraction of bronchial smooth muscle and submucosal oedema [1].

Because exercise initiates the endogenous release of mediators associated with inflammation that cause the airways of asthmatics to narrow, the severity of EIA is thought to be a reflection of airway inflammation.

Exercise challenge was promoted by Godfrey and colleagues in the 1970s, to identify drugs useful in the treatment and prevention of asthma [3–6]. EIA was also used to study the duration of the protective effect of drugs [6, 7]. Many of the early drug studies have been summarized previously [1]. Several studies involved the investigation of the acute effect of a single dose of drug at a time when lung function was poor with FEV1, less than 75% predicted. Furthermore, the doses of some drugs, in particular, the antihistamines and anticholinergics, were limited by unwanted side-effects. However, there were clear indications arising from these early studies. Firstly, the β-adrenoceptor agonists given by inhalation were demonstrated to be the most effective against EIA, particularly in patients with airflow limitation before exercise. In patients with normal lung function, EIA could be prevented very effectively by sodium cromoglycate, but the dose required varied between patients. For patients with severe EIA, doubling the dose of β-adrenoceptor agonist or sodium cromoglycate, or using them in combination, was shown to be effective. Anecdotal reports demonstrated that the addition of an anticholinergic could be useful in severe cases, although used alone this class of drug had a variable effect on EIA. The sedating antihistamines, when given by usual routes of administration (inhalation or intra-muscular), were also shown to have some benefit. Although there were controversial reports on the use of bronchodilator drugs given as tablets, it was generally accepted that the effect of the same drug given by inhalation was superior. It was also recognized that drugs given by inhalation had a short protective effect against EIA, usually less than two hours.

The study by Finnerty and Holgate [8], reported in this issue of the Journal, and those of Combs et al. [9] and Fuglsang et al. [10] reported in a recent issue, serve to highlight some important points about the investigation of EIA and the use of drugs to control it.

The study by Finnerty and Holgate [8] demonstrate how drugs given in the right dose can be used to study the mechanism of EIA. The studies of Combs et al. [9] and Fuglsang et al. [10] provide clear information as to which drugs do and do not prevent EIA. All of the studies demonstrate that severe EIA can occur despite the presence of good basal lung function.

Finnerty and Holgate [8] have chosen to study an unusual combination of drugs given in a high dose; an anticholinergic, ipratropium bromide (500 μg), and an antihistamine, terfenadine (180 mg). The study of 10 subjects demonstrated effective inhibition of EIA in seven subjects, using this combination. The preventive effect of the two drugs on EIA appeared to be additive. Given as a single medication, ipratropium bromide was effective in reducing the severity of EIA by close to 50% in 5 out of 10 subjects, the same proportion of subjects previously recognized to benefit from a lower dose of the drug [1]. By contrast, terfenadine caused a 50% inhibition of EIA in

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only 1 of the 10 subjects. Although the true additive effect of the combination of ipratropium bromide and terfenadine was seen clearly in only three subjects, the benefit of the combination was demonstrated for the group. Protection was unrelated to improvement in pre-exercise lung function induced by the drugs. The authors conclude “that both histamine and vagal stimulation contribute independently and additively to EIA” and it is unlikely that a major component of the bronchoconstriction produced by the release of histamine in EIA was through vagal stimulation.

The findings of this study provide some insight into the mechanism of EIA. The conclusion that EIA is a result of two or more events (histamine release and, independently, vagal stimulation) could account for the variable effects found with antihistamine and anticholinergic agents in the past. It may also account for the clear benefit of β₂-adrenoceptor agonists and sodium cromoglycate, drugs that have actions at multiple sites, including mast cells, nerves and smooth muscle.

The doses of the drugs used by Finnerty and Holgate [8] were high, and it is doubtful that this combination would be administered clinically, except in cases of severe EIA. Even trying to avoid the prophylactic use of β₂-adrenoceptor agonists is unlikely to result in either terfenadine or ipratropium bromide being used in combination as a first line therapy for prevention of EIA.

For this reason, the study of Coms et al. [9], demonstrating the efficacy of sodium cromoglycate and nedocromil sodium in EIA, is important. The children they studied had been institutionalized at high altitude for 3 months, for their asthma. Their regular treatment with steroids and sodium cromoglycate had been withdrawn for at least one week before the study. They had reasonably good lung function (89% of predicted normal) but moderately severe EIA, 36±13.5 (so) % fall in FEV₁.

There are several points to highlight in this study. Firstly, the investigators demonstrated the reproducibility of EIA in their subjects, an important factor when assessing the efficacy of a drug and often overlooked by investigators. Secondly, they compared the effect of sodium cromoglycate (10 mg) and nedocromil sodium (4 mg) in the same subjects, and demonstrated that these drugs were equally effective; few studies have made this comparison. Finally, they demonstrated that in subjects with good coordination there is no advantage in using a spacing device, when the drugs used have no unwanted effects or are not absorbed systemically.

Sodium cromoglycate has been marketed for more than 20 yrs, and has a reputation as a safe drug that can be used many times in a day being equally effective against EIA in both adults and children. It was perhaps unfortunate that the dose of 20 mg originally used in the spinacap could not easily be administered from a pressurized metered dose inhaler. Thus, the dose of sodium cromoglycate often used today, i.e. 2×5 mg per inhalation, is much less than that in the original studies. Sodium cromoglycate may have been shown to be superior to nedocromil had it been given in the originally recommended dose of 20 mg, and immediately before, rather than 30 min before, exercise. From the data of Coms et al. [9], there seems to be no advantage in replacing sodium cromoglycate with nedocromil sodium for prevention of EIA. This study also demonstrated that drugs that do not affect baseline lung function, i.e. without bronchodilating properties, are effective in preventing EIA.

By contrast, the study of Fuglsang et al. [10] clearly demonstrated that the β₂-adrenoceptor agonist terbutaline, when given twice daily as a sustained release formulation in a daily dose of 4, 8 or 12 mg, was unable to reduce significantly the fall in FEV₁ after exercise. This confirms the early studies, using a single dose of 5 mg of terbutaline given 90 min before exercise [1, 7], and extends them to demonstrate that chronic treatment with higher doses, attaining high plasma levels of drug and good lung function, is still not accompanied by efficacy in EIA.

This finding should put to rest any controversy remaining about the usefulness of bronchodilator drugs given orally for EIA, or to prevent attacks of asthma provoked by other stimuli [1]. Their only advantage is that they produce good lung function, and, thus, whilst there is still a fall in FEV₁ in response to a stimulus, the lung function may still be good enough to avoid the severity of symptoms previously experienced.

So, what do we do to prevent EIA in the context of modern day treatment of asthma? For patients who have normal lung function and whose asthma symptoms are controlled by daily use of sodium cromoglycate or nedocromil sodium, it may be suggested that additional doses be used immediately before exercise. It is important to establish the dose of these drugs that will prevent EIA, and this can be done in a laboratory or by the patient. For sodium cromoglycate, the 20 mg dose originally recommended will be effective for most. Some patients may require only 5 or 10 mg, and others 40 mg [11]. Similarly, the dose of nedocromil may need to be increased to control EIA. Acknowledging that the protective effect of these drugs against EIA is likely to be less than 2 h, the dose should be repeated if this interval occurs between dosing and exercise.

The same prescription can be used for patients who are taking inhaled steroids for control of asthma, but who still suffer EIA. It is important to ask patients who have normal lung function, no symptoms, and no day-to-day variability of lung function whether they avoid strenuous exercise because it provokes symptoms of asthma. For example, we felt no need to make daily treatment with beclomethasone dipropionate one of the exclusion criteria in drug trials involving EIA. Indeed many subjects taking aerosol steroids have asthma provoked by exercise [12, 13]. However, a recent report in children [14] demonstrated that budesonide reduced severity, but 11 or the 16 children still had EIA after 3 weeks of treatment.

From the results of a recent study using hyperosmolar stimuli, we were impressed by the preventative effect of the combination of nedocromil sodium and sodium cromoglycate with aerosol steroids [15, 16]. From these studies we would predict this combination would also be most effective for the prevention of exercise-induced asthma.

The prophylactic use of β₂-adrenoceptor agonists, given as aerosols, should be reserved for those patients who have airflow limitation before exercise, and for those in whom...
adequate doses of sodium cromoglycate or nedocromil sodium are still ineffective. Because the protective effect of the short acting \( \beta_2 \)-adrenoceptor agonists is usually less than 2 h, it seems inadvisable, in view of the current debate on these drugs, to recommend multiple uses in a day. Whilst the newer long-acting \( \beta_2 \)-adrenoceptor agonists, such as salmeterol or formoterol, may delay long-protection to some subjects, this is not true for all patients [12]. Beta-2-adrenoceptor agonists are the only drugs that will affect recovery from EIA, and for this reason they are recommended as rescue medications.

For some patients, particularly young adults, EIA is the only manifestation of their asthma. Many of these patients still suffer EIA while taking aerosol steroids [13, 17] and are unwilling to accept chronic treatment with or higher doses of steroids in order to control their bronchial hyperresponsiveness. For these patients, the severity of EIA may vary widely. To control EIA, sodium cromoglycate or nedocromil sodium, or a \( \beta_2 \)-adrenoceptor agonist may be given alone, or in combination, before exercise. For those with severe EIA uncontrolled by this therapy, an anticholinergic, such as ipratropium bromide, or the antihistamine, terfenadine, can be added.

**References**


16. **Anderson SD, du Toit JI, Rodwell LT, Jenkins CR.** - The acute effect of sodium cromoglycate on airway response to hyperosmolar saline (4.5%) before and during treatment with inhaled steroids. ERJ (abstract in press).