Beta$_2$-agonists for exercise-induced asthma

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In the current issue of the *Journal*, we feature the Cochrane Review on effects of inhaled beta$_2$-agonists in the pretreatment of children and adults with exercise-induced asthma. We asked Dr W Gary Smith to comment on and put the review in context.

BETA$_2$-AGONISTS FOR EXERCISE-INDUCED ASTHMA

Background

It is well known that physical exercise can trigger asthma symptoms and can induce bronchial obstruction in individuals without clinical asthma. International guidelines on asthma management recommend the use of beta$_2$-agonists at any stage of the disease. At present, however, no consensus has been reached about the efficacy and safety of beta$_2$-agonists in the pretreatment of exercise-induced asthma and exercise-induced bronchoconstriction. For the purpose of the present review, both of these conditions are referred to by the acronym 'EIA', independent of the presence of an underlying chronic clinical disease.

Methods

Search strategy: Trials were identified by electronic search of the Cochrane Airways Group Specialised Register of Trials and by manual search of respiratory journals and meetings. Searches are current as of August 2013.

Selection criteria: Randomized, double-blinded, placebo-controlled trials of any study design, published in full text, that assessed the effects of inhaled beta$_2$-agonists on EIA in adults and children were included. Studies that did not clearly state diagnostic criteria for EIA were excluded.

Data analysis: Standard methodological procedures were used as outlined by The Cochrane Collaboration.

Results

Fifty-three trials involving a total of 1139 participants were included. Forty-eight studies used a crossover design and five were performed in accordance with a parallel-group design. Forty-five studies addressed the effect of a single beta$_2$-agonist administration and eight focused on long-term treatment. These two intervention regimens were addressed using different comparisons.

Among primary outcomes for short-term administration, data on maximum fall in forced expiratory volume in 1 s (FEV_1) showed a significant protective effect for both short-acting beta-agonists (SABA) and long-acting beta-agonists (LABA) compared with placebo, with a mean difference of −17.67% (95% CI −19.51% to −15.84%; P=0.00001 [799 participants from 72 studies]). The subgroup analysis of studies performed in adults compared with those performed in children showed high heterogeneity confined to children, despite the comparable mean bronchoprotective effect.

Secondary outcomes involving other pulmonary function parameters confirmed a more positive and protective effect of beta$_2$-agonists on EIA compared with placebo. Occurrence of side effects was not significantly different between beta$_2$-agonists and placebo.

Overall evaluation of the included long-term studies suggests a beta$_2$-agonist bronchoprotective effect for the first dose of treatment. However, long-term use of both SABA and LABA induced the onset of tolerance and decreased the duration of drug effect, even after a short treatment period.

Conclusions

Evidence of low to moderate quality shows that beta$_2$-agonists, both SABA and LABA, are effective and safe in preventing EIA when administered in a single dose.

Long-term regular administration of inhaled beta$_2$-agonists induces tolerance and lacks sufficient safety data. This finding appears to be of particular clinical relevance in view of the potential for prolonged regular use of beta$_2$-agonists as monotherapy in the pretreatment of EIA, despite the warnings of drug agencies (Food and Drug Administration, European Medicines Agency) regarding LABA.

The full text of the Cochrane Review is available in The Cochrane Library (1).

The review uses the acronym 'EIA' to refer to the diagnosis of both exercise-induced bronchospasm (EIB) and exercise-induced asthma (EIA). Clearly, the latter would be used in children with a known diagnosis of asthma. The differential diagnosis of EIB would include vocal cord dysfunction, exercise-induced laryngomalacia and exercise-induced hyperventilation. EIA has a reported incidence of up to 90% in asthmatic children; conversely, EIB appears to occur primarily in elite cold-weather athletes, with an incidence of 9% to 12% in adolescent athletes. Two main theories attempt to explain the EIB phenomenon: the thermal or heat-loss hypothesis, and the osmotic or water-loss hypothesis. Practically, testing for EIA is not necessary because exercise is an expected trigger. Exercise testing to diagnose EIB should be performed by an experienced technologist, recognizing that child elite athletes have high levels of tolerance for exercise (2).

Most clinicians would recommend the SABA salbutamol (200 µg) 15 min before significant exercise that triggers bronchospasm. However, the protective effect lasts only 1 h to 3 h, and daily use can attenuate the degree of protection and promote tolerance (3). EIA should never result in a limitation of sport activities. However, obesity is significantly more common in adolescents with 'not well' and 'very poorly' controlled asthma, suggesting that EIA often interferes with exercise (4).

Regular need for a reliever to prevent or treat exercise-induced symptoms indicates suboptimal control of asthma. Suboptimal control of asthma (≥4 doses per week of SABA) mandates the use

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of daily inhaled corticosteroids (ICS). Fast-acting beta agonists in Canada include salbutamol, terbutaline and one long-acting beta agonist, formoterol, which should only be used concomitantly with an ICS (5).

A combination product exists that includes an ICS and formoterol (LABA) and has been marketed for use as a reliever medication in self-management for acute loss of control. Due to concerns regarding tolerance and extra unintended doses of ICS, recent Canadian guidelines for children recommend the use of a SABA alone for this condition (6).

Alternative treatments for EIA have been considered, especially for elite cold-weather athletes. Warming up before activity results in a refractory period during which EIA is unlikely to occur. Wearing heat masks specially designed for outdoor winter athletes may protect against bronchospasm triggered by cold, dry air (7).

Dietary and nutritional therapies have not been well supported (8,9).

If a clinician is treating a competitive athlete with EIA who will be pretreated with a SABA, the website for The Canadian Centre for Ethics in Sports (www.cces.ca) should be reviewed to avoid the use of a prohibited therapy. Salbutamol and formoterol are designated 'Global Drug Reference Online' (essentially, for salbutamol, treatment must be limited to a maximum of 1600 µg per 24 h) and terbutaline is prohibited.

This Cochrane review should be useful for clinicians who are treating EIB in the short term.

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