COMBINATION OF INHALED STEROID AND LONG-ACTING BETA-2-AGONIST THERAPY — USE AND LIMITATIONS

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ABSTRACT
The combination of inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABAs) has an important place in new asthma guidelines as an option for asthma that is not controlled on low- or medium-dose ICS after consideration has been given to adherence and technique. The rationale for their use is due to both complementary and synergistic mechanisms of action. Combination therapy may have different efficacy in different age-groups and, because of patient variability, it may not always be the most effective treatment modality. The addition of LABAs to ICS (or combination therapy) is not first-line therapy and should be restricted to patients who truly need them. LABAs are not recommended for children under the age of 5. Patients on combination therapy should be weaned off the LABA when control is achieved. LABAs should never be used as monotherapy. Single inhaler use of LABAs administered sequentially in separate inhalers from ICS is prone to possible misuse. Fixed-dose combination products are thus preferred as they avoid this possibility.

MECHANISM OF ACTION OF BETA-2-AGONISTS
Beta-2-agonists (β2-agonists) bind to G-protein cell surface β2-receptors, resulting in increased intracellular cyclic adenosine monophosphate (cAMP). Short-acting β2-agonists (SABAs), such as salbutamol, fenoterol and terbutaline, are the most widely used asthma drugs. They are first-line relief therapy and for mild intermittent cases they are the only drug needed. They have a rapid onset of action but their effects wear off over 4-6 hours, i.e. they are rapid but short-acting bronchodilators.

The long-acting β2-agonists (LABAs), salmeterol and formoterol, cause sustained relaxation of airway smooth muscle and thus bronchodilation for at least 12 hours. In addition LABAs reduce bronchial hyperresponsiveness to both specific and non-specific bronchoconstrictive stimuli. Non-bronchodilator effects include inhibition of the release of inflammatory mediators such as histamine and cysteinyl leukotrienes from mast cells and prevention of plasma exudation. β2-agonists also inhibit extracellular matrix protein release from airway fibroblasts, a protein that contributes to airway wall thickening and increased width of the basement membrane.

While both salmeterol and formoterol have similar duration of activity they differ in many important respects. There is controversy about the mechanism of prolonged action of LABAs. Salmeterol’s long, lipophilic side chain may bind to exosites near β2-receptors, allowing the active portion of the molecule to remain at the receptor site, continually binding and releasing, whereas formoterol may exert its long duration of action primarily by dissolving in the cell membrane and acting as a ‘slow-release’ formulation. The differences in LABAs’ onset of action are probably mediated by differences in lipophilicity. Salmeterol exerts its bronchodilator effects within 10-20 minutes and is thus appropriate for use as maintenance therapy along with ICS but not for rapid reversal of airflow obstruction or for treatment of acute asthma symptoms. The onset of bronchodilation of formoterol is within 5 minutes, close to that of SABAs (2-3 minutes). Although combination ICS/LABA using formoterol may be given for both symptom relief as well as chronic treatment of asthma it is most important to note that single inhaler LABAs are not recommended for acute treatment of bronchodilation, rather as controller treatment, and must always be given in conjunction with ICS.

ADVERSE EFFECTS OF β2-AGONISTS
Side-effects of β2-agonists are greatest when they are administered orally or parenterally, whereas pharmacologically predictable effects are seen when they are given via the inhalational route are usually of little clinical significance. Common side-effects include tremor, tachycardia and palpitations. Hypokalaemia, hypomagnesaemia and hyperglycaemia may occur with overdosage.

Desensitisation, downregulation, increased responsiveness and loss of bronchoprotection
Long-term stimulation with β2-agonists leads to receptor desensitisation and downregulation. Mechanisms of desensitisation include uncoupling of receptors from adenylate cyclase, internalisation of uncoupled receptors and phosphorylation of internalised receptors. Chronic use of SABAs over a period of days or weeks leads to desensitisation to their continued effects, with an effect primarily of reducing the duration of bronchodilation rather than the peak effect. Furthermore, after cessation of regular treatment with SABAs after chronic use, patients may experience rebound increases in bronchial responsiveness. A similar effect has not been seen after cessation of treatment with LABAs.

Loss of bronchoprotection (the ability of pretreatment with β2-agonists to protect bronchoconstriction from stimuli such as exercise, histamine, methacholine, etc.) has been documented with chronic use of both short-acting and long acting β2-agonists. Protection is reduced from its original level but not completely lost. Most importantly, concerns have been raised over the long-term use of LABAs and whether this leads to clinically significant reductions in the efficacy of SABAs when used for rapid relief of symptoms. This has not been borne out in an open study, a placebo crossover study and an emergency department based study.

MECHANISM OF ACTION OF ICS
Corticosteroids act intracellularly by binding to the glucocorticoid receptor (GR). The steroid-receptor complex is transported to the nucleus where it binds directly to specific DNA sequences and also interacts with other
DNA-binding transcription factors leading to decreased transcription of pro-inflammatory mediators such as interleukin-4 (IL4) and IL5, intercellular adhesion molecule 1 (ICAM-1) and E-selectin. This reduces the number and activation status of inflammatory cells in the lumen and tissues of the airways.

**INTERACTIONS BETWEEN LABAs AND ICS**

The major effects of LABAs and ICS are complementary, affecting different aspects of the pathophysiology of asthma. LABAs predominantly address the smooth-muscle dysfunction, reducing bronchoconstriction, bronchial hyper-reactivity and inflammatory mediator release. ICS predominantly address the airway inflammation with resultant cellular infiltration and activation, mucosal oedema and cellular proliferation. However, there are also potent interactions between ICS and LABAs which make their actions synergistic as well as complementary.

**LABAs → ICS**

LABAs have marked influences on the GR. They ‘prime’ the GR for LABA binding by rendering the receptor more sensitive to steroid-dependent activation. In addition they increase the rate of translocation of GRs to the nucleus, thus enhancing the action of glucocorticoids. They also (along with SABAs and glucocorticosteroids themselves) increase the effect of dampening down pro-inflammatory mediators when the GR binds to DNA sequences in the nucleus.

**ICS → LABAs**

Corticosteroids modulate β2-receptors and their function. They stimulate the genes responsible for transcription of β2-receptors, increasing the density of available β2-receptors. Chronic inflammation itself, as well as the chronic use of β2-agonists causes down-regulation of β2-receptors. Administration of ICS protects the receptors from both inflammation and β2-agonist-mediated down-regulation as well as inflammation-mediated receptor uncoupling. ICS also increase the efficacy of coupling between β2-agonists and the β2-receptor leading to more efficient release of downstream events and more effective action.

**LABAs’ PLACE IN GUIDELINES**

ICS are universally recognised as the most effective treatment for asthma. When ICS on their own fail to control symptoms, other options include increasing the dose of ICS or adding additional controller medication such as a LABA, a leukotriene receptor antagonist (LTRA) or theophylline. Guidelines from different parts of the world differ on when they recommend increasing the dose of ICS or adding additional controller medication such as a LABA, a leukotriene receptor antagonist (LTRA) or theophylline.

Subsequent to the meta-analysis an additional study was published in the *New England Journal of Medicine*, which is usually referred to as the BADGER (best add on therapy giving effective responses) trial. The trial participants were children 6-17 years old already on 100 µg fluticasone bid with uncontrolled asthma. They were randomised to ICS step-up (fluticasone 50 µg bid), LABA step-up (fluticasone 100 µg bid with salmeterol 50 µg bid) or LTRA step-up (fluticasone 100 µg bid with montelukast 5 mg or 10 mg daily). The study used a triple cross-over study design and 3 outcome measures: exacerbations, asthma control days and lung function testing. In this study nearly all children had a differential response to therapy. LABA step-up was most likely to be the best response as compared to LTRA step-up (relative probability 1.6, 95% confidence interval (CI) 1.1-2.3) and ICS step-up (relative probability 1.7; 95% CI 1.2-2.4). Better control at baseline predicted a better response to LABA step-up.

**SAFE AND UNSAFE USE OF LABAs**

Concerns have been raised regarding the long-term use of β2-agonists.

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**Single inhaler controller/reliever therapy**

A recent Cochrane review has analysed the evidence for the addition of LABAs to inhaled steroids versus higher-dose inhaled steroids in adults and children with persistent asthma. Forty-eight studies were included, 40 in adults only, 6 in children only and 2 in adults and children. Participants had inadequate control of their asthma at the time of enrolment in all but 3 studies, but 2 of the paediatric trials failed to report baseline severity. Treatment with combination therapy was associated with a lower risk of exacerbations (by about 12%), and significantly greater improvement from baseline in lung function, morning and evening peak flows, symptoms, symptom-free days and rescue medication use than treatment with higher ICS dose. The authors of the review state that the limited paediatric trials means that there are insufficient data to comment firmly on a differential effect associated with age; however in this meta-analysis there was a trend towards increased exacerbations and hospitalisation in children on combination therapy.

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**EVIDENCE FOR RECOMMENDATIONS IN CHILDREN AND ADULTS**

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Asthma mortality
When overused, the SABAs have been associated with increased asthma mortality. An epidemic of deaths among asthmatics in the UK between 1959 and 1966 was associated with the use of a strong MDI formulation of the non-selective $\beta_2$-agonist isoprenaline and in the mid-1970s fenoterol was associated with a similar epidemic in New Zealand. In addition, for over 15 years, there has been concern about paradoxical increases in asthma-related deaths in patients with uncontrolled asthma treated with LABAs. In the Serevent Nationwide Surveillance Study, patients treated with salmeterol as opposed to salbutamol in addition to their usual asthma therapy showed an excess mortality especially in those with severe asthma on entry. Patients who died had asthma that should have been more appropriately treated by earlier and higher doses of ICS. A further 2 studies found no evidence of adverse events in patients receiving salmeterol. Recent Cochrane reviews on asthma therapy with LABA or ICS showed no significant differences in fatal or non-fatal adverse effects due to LABA combination therapy.

In 2005 the USA Food and Drug Administration (FDA) issued a ‘black box’ warning on LABA use in response to the results and early termination of the SMART study. The SMART study was designed to assess the safety of salmeterol but was halted after an interim analysis revealed excess mortality and life-threatening respiratory events in the active treatment group. In the SMART study subjects attended only a single initial clinic visit to have their eligibility assessed and to be randomised. Subjects were given 7 canisters of salmeterol or placebo to be used with metered-dose inhalers (MDIs) and instructed to use 2 inhalations twice daily in addition to their usual therapy. No further clinic visits were scheduled and subsequent follow-up was conducted by telephone every 4 weeks without reinforcement of compliance with study or baseline medication. Over 26 000 subjects took part. The population had poorly controlled asthma with visits to emergency rooms and hospitalisations reported in 26% and 8% of patients respectively during the previous year; 61% had nocturnal symptoms at least weekly. Less than half the population reported using ICS. African-Americans made up about 18% of the subjects; they had more severe disease, and only 38% were using ICS.

Despite this not being the aim, the study population were thus overwhelmingly poorly controlled asthmatics, many taking LABAs without any ICS.

Statistically significant differences were noted in the end points of asthma-related relative risk (RR) 4.37, 95% CI 1.25-15.34 deaths and combined asthma-related death or life-threatening episodes (RR 1.71, 95% CI 1.01-2.89). These differences were largely driven by the African-American population. No statistically significant differences were noted in the white population in any end point. The possibility exists that there are genetic differences in responses to medication between African-Americans and the American white population (most notably a higher arg-arg genotype for nucleotide at position 16 of the $\beta_2$-adrenergoreceptor leading to relative $\beta_2$-tachyphylaxis); however a more likely explanation is the very low rate of ICS use in the African-American study population.

Post hoc analysis revealed that using ICS had a powerful effect on results. No significant differences were noted in the primary or secondary event rates for the overall population reporting baseline use of ICS. Similarly, for the African-American population, statistically significant differences were noted only in those reporting no baseline use of ICS.

Asthma control
LABAs should never be used as monotherapy for asthma. The Salmeterol or Corticosteroids Study (SOSC) compared the inhaled corticosteroid triamcinolone with salmeterol monotherapy and placebo and found lower rates of treatment failures and exacerbations in the corticosteroid group. The lack of effectiveness of LABA monotherapy was confirmed by 2 studies in children that compared salmeterol with beclomethasone. The Salmeterol + Inhaled Corticosteroids (SLIC) study recruited patients with documented adherence to ICS (triamcinolone) and added a LABA (salmeterol) to achieve a group controlled with combination therapy. Subjects were then randomised to reduce the ICS by 50% or to taper and eliminate the ICS dose completely. This trial showed that patients with moderate to severe asthma who achieve control on combination therapy can safely be weaned to a 50% corticosteroid dose reduction, but that further weaning and elimination of corticosteroids (LABA monotherapy) was associated with treatment failure as measured by lung function worsening, increase in rescue therapy, systemic corticosteroid use or physician clinical assessment of loss of control.

Because of these studies showing the danger of LABA monotherapy, the USA FDA has required drug label changes on all USA-manufactured LABAs. These are now required to contraindicate the use of LABA monotherapy (without concomitant administration of an ICS) and recommend stopping the use of a LABA once asthma control is achieved while continuing other asthma controller medication such as ICS. They recommend against the use of a LABA in patients in whom asthma is controlled with low- or medium-dose ICS. Finally they recommend that fixed-dose combination products be used preferentially to separate inhalers to ensure concomitant ICS therapy and the inadvertent overuse of LABA monotherapy.

ADHERENCE WITH COMBINATION THERAPY
A small study in the UK found patients on ICS/LABA inhalers had significantly greater adherence compared to those on ICS alone (72.2% v. 40.5%). Reasons for this effect are pure speculation, but might include a perceived benefit from taking the inhaler with the LABA as a result of the symptom relief afforded by the bronchodilation.

When assessed by medication refill rates, adherence to combination LABA and ICS in a single inhaler is 30-73% higher than that of combination therapy using two separate inhalers. However medication adherence is extremely difficult to measure, as patient reports and canister weighing and floating are known to be inaccurate. Most users of MDIs do not keep track of how many doses are still available in their device. Most pMDI users only consider their asthma pump empty when nothing further comes out of the inhaler, which does not take account of the progressive tailing off of nominal dose once the number of labelled doses has been exceeded. Therefore dose counters have been recommended as a critical aspect of the design of the ‘ideal inhaler’. The optimal method of assessment of adherence uses covert electronic monitoring (and time recording) of device actuation. The first randomised controlled group using this methodology recruited only 111 subjects. The mean adherence was 73.7% for the ICS, 76.7% for the LABA, and 82.4% for the combination product. Although these differences were not statistically significant the differences may have been underpowered. In 2 (4%) of the 49 subjects who were supposed to be using LABA and ICS dual therapy by two separate inhal-
ers, the LABA was effectively taken as monotherapy during a 6-week period.

CONCLUSION

LABA and ICS have complementary and synergistic effects. Large systematic reviews have shown better control in adults on LABA/ICS combinations when compared with higher-dose ICS. Sufficient paediatric studies are still lacking but a recent crossover study shows better response to LABA/ICS therapy than double-dose ICS or ICS/LTRA therapy. LABA monotherapy is dangerous and associated with excess mortality. LABAs should only be used as combination therapy along with ICS and never as monotherapy, and should be limited to those patients who truly need them as an option for asthma that is not controlled on low- or medium-dose ICS after consideration has been given to adherence and technique. Combination products are preferable to co-administration by one single inhaler as they may allow better efficacy by simultaneous deposition of synergistic molecules and separate inhalers have the capacity to allow inadvertent or purposeful LABA monotherapy. All asthma devices should preferably have built-in dose counters. When used appropriately combination LABA/ICS products are an important component of the treatment of moderate and severe asthma.

Declaration of conflict of interest


REFERENCES