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Safety of Combination ICS/LABA Therapy for Chronic Asthma

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Introduction

Current therapeutic approaches for chronic maintenance treatment in asthma support the addition of a long-acting β-agonist (LABA) to an inhaled corticosteroid (ICS). Notably, substantial clinical evidence attests to a potential risk of asthma mortality associated with LABAs when prescribed as monotherapy without concomitant ICS or scheduled medical review.[1-10] In view of this potential risk, asthma guidelines recommend that LABAs should always be taken with the steroid, either in a single device or as separate inhalers.[11-16] Important benefits are associated with combination ICS/LABA inhalers over the separate inhalers; a combination inhaler could reduce asthma mortality by increasing compliance with steroid, by increasing the prescription of steroids, and by reducing the risk of death from asthma that is associated with LABA monotherapy. Peer-reviewed clinical trial evidence is presented with accompanying expert commentary. This publication is intended to be an educational resource for health care professionals.

ICS/LABA therapy in chronic asthma

Internationally accepted guidelines with proposed goals for asthma treatment and management accept the addition of a LABA to an ICS as effective therapy in persistent asthma.[11,12] However, despite there being effective medications and several evidence-based recommendations,[13-16] recent patient surveys of asthma management practices in New Zealand[17,18] and worldwide (the Asthma Insights and Reality in Europe [AIRE] survey;[19] the Asthma Insights and Reality in Asia-Pacific [AIRIAP] survey;[20] and surveys conducted in Canada[21,22] and the US[23]) show that asthma is poorly controlled around the world. These surveys highlight the fact that asthma is underdiagnosed and undertreated, and that there is considerable room for improvement in asthma control, although ICS have had a positive impact on the day-to-day management of asthma.

Current global/local management approaches

The Global Initiative for Asthma (GINA) guidelines, regarded as the most authoritative road map for asthma care, offer a framework to achieve and maintain asthma control.[16] Overall asthma control is defined by GINA as:

- Current control: relief of symptoms, rescue or reliever use, maintaining activity and lung function,
- Reduction of future risk: preventing exacerbations, irritability/worsening, loss of lung function over time, and medication side effects.

GINA advises that for ongoing management of asthma, clinicians should constantly evaluate the level of asthma control in their patients, by questioning them about their status according to asthma symptoms and, if relevant, PEF or FEV_1.

GINA encourages clinicians and patients to collaborate on a medically appropriate and practical written personal asthma action plan, to reinforce the goal of asthma control. The Asthma and Respiratory Foundation of New Zealand provides adult and child self management plans that may be personalised for patients; these are available from the Foundation's website (www.asthmanz.co.nz).

Five-step treatment guideline

GINA treatment recommendations for adults and children aged >5 years are based on a five-step approach, matching treatment with level of asthma severity.[11,16] Step 1 is as-needed rapid-acting inhaled β_2-agonist. The other four treatment steps include a preventer option, ranging from low-dose ICS as the preferred treatment option at Step 2, to high-dose ICS plus LABA combinations together with oral corticosteroids at Step 5. Once the level of asthma control has been established, GINA recommends reducing the amount of treatment. When asthma remains uncontrolled, treatment needs to be increased to the next step.

GINA advises that the available literature on treatment of asthma in children aged ≤5 years precludes detailed treatment recommendations. However, local guidelines on the diagnosis and management of asthma in children aged 1–15 years and those under 5 years are provided by the Paediatric Society of New Zealand (www.paediatrics.org.nz). The Society notes that few infants who wheeze have asthma. The guidelines advise that during acute episodes of recurrent or persistent wheeze, supportive treatment should be provided to children as described under management of acute wheeze. In individual cases a trial of bronchodilators may be considered. Regular daily ICS treatment may be indicated for the small group of infants considered to have asthma.

In the GINA treatment categories, adults and children >5 years of age in Step 1 only need a rescue inhaler occasionally, once or twice a week at the most. Patients in Step 2 only need low doses of ICS once or twice daily to achieve really good asthma control (preventing symptoms and attacks).

Clinical trial data have shown that low-dose corticosteroids alone may not provide enough asthma control.[24] In the Gaining Optimal Asthma ControL (GOAL) trial, patients aged ≥12 years and <90 years with uncontrolled asthma across a wide range of severities were assigned to treatment with fluticasone propionate alone or in combination with salmeterol. Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved comprehensive, guideline-defined control with combination inhaled therapy than those given increasing doses of fluticasone alone.

The most common reason for difficult-to-control asthma is due to lack of adherence or poor inhaler technique, which is of huge concern in chronic asthma; many patients tend not to use their medications in the absence of symptoms.

For those patients that really are using their maintenance medications, the preferred treatment as stated by GINA for adults and children >5 years at Step 4 is to combine a medium or high dose of ICS with a LABA (for those aged ≤5 years, high-dose ICS plus add-on therapy if needed). However, in most patients, increasing from a medium dose to a high dose of ICS provides relatively little additional benefit. The high dose is recommended only on a trial basis for 3 to 6 months in cases where asthma cannot be controlled with a medium-dose ICS plus a LABA. Adding oral corticosteroids to other controller medications may be effective but can cause severe side effects and should be considered only if the asthma remains severely uncontrolled on Step 4 medications.

Risks of LABA monotherapy in asthma

Despite the fact that LABA therapy offers a recognised clinical benefit, considerable controversy exists regarding the safety of LABAs,[1-4] particularly because of the evidence suggesting that they might increase the risk of asthma mortality when used by patients with unstable asthma without concomitant ICS or scheduled medical review.[5-10]

These safely concerns have recently resulted in the United States Food and Drugs Administration (FDA) mandating label changes impacting LABA use in the USA,[25] and requesting new studies of their efficacy and safety. Following its comprehensive review of the benefits and harms of using LABAs to treat asthma, the FDA concluded that the benefits of LABAs continue to outweigh the risks when the drugs are used appropriately and that LABAs should remain available for the treatment of asthma. The drug-label changes emphasise the seriousness of the risk associated with LABA monotherapy; their specific advice is as follows:

1. the use of LABAs without the use of an asthma preventer medication such as an ICS is contraindicated in the treatment of asthma;
2. LABAs should be reserved for use as additional therapy for patients whose asthma symptoms are not adequately managed by asthma preventer medication, such as an ICS;
3. until additional data are available from large clinical trials evaluating the safety of LABA coadministration with an ICS, LABAs should be used for the shortest period of time required to achieve control of asthma symptoms and then withdrawn, if possible, once asthma control is achieved; patients should then be maintained if possible on asthma preventer medication;
4. paediatric and adolescent patients who require the addition of an LABA to an ICS should use a combination ICS/LABA product to ensure adherence to both medications in these age groups.

Some respiratory specialists have called for the withdrawal of LABAs for use in asthma as single-inhaler therapy and for LABA use to be restricted to concomitant use with an ICS.[43]

LABA monotherapy should not be substituted for an ICS.[44] (see last page)

The addition of LABAs to ICS in asthma

In 2000, a meta-analysis systematically examined the clinical benefits of adding salmeterol compared with increasing the ICS dose.[26] It concluded that the addition of salmeterol in symptomatic patients aged ≥12 years receiving low to moderate ICS doses improves lung function and increases the number of days and nights without symptoms or need for rescue treatment, with no increase in exacerbations of any severity.

Advantages of combination ICS/LABA therapy

- The GOAL study involved 3,421 patients with uncontrolled asthma and compared the efficacy and safety of fluticasone propionate with or without salmeterol in achieving two rigorous, composite measures of control: totally controlled and well-controlled asthma, as according to the GINA and National Institutes of Health treatment guidelines.[24] In each treatment stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users), significantly more patients achieved well-controlled and totally controlled asthma with salmeterol/fluticasone than with fluticasone alone. In addition, the combination treatment group achieved control more rapidly and at a lower ICS dose than the monotherapy group. Compared with fluticasone alone, combination therapy was associated with significantly fewer exacerbations requiring oral corticosteroids and/or hospitalisation or emergency visits, significantly higher quality of life scores, and significantly higher FEV_1.
- A recent Cochrane review compared the effect of LABA with ICS versus a higher dose of ICS alone on the risk of asthma exacerbations, lung function, and other measures of asthma control.[27] The combination was modestly more effective in reducing exacerbations requiring oral corticosteroids, and provided greater improvement in lung function, symptoms, and use of rescue β-agonists.
- A recent systematic literature review and meta-analysis of observational studies in clinical practice patients has shown that patients treated with a single-inhaler containing ICS plus LABA experienced fewer exacerbations (measured as asthma-related hospitalisations and/or emergency room visits) compared with patients treated with ICS alone.[28]
- Poor adherence with asthma treatments is undoubtedly a major contributor to the poor outcomes that are consistently seen in surveys of patients with asthma,[29-33] as demonstrated in a recent New Zealand study which showed that, when adherence is defined as taking at least 90% of prescribed doses of twice-daily ICS, adherence was less than 20% in a motivated group of patients who had volunteered to take part in a clinical study.[34]
- Combination ICS/LABA inhalers have the potential to improve adherence with long-term asthma treatment, by reducing the number of inhalers that patients have to take.[35] In addition, the short-term improvement in symptoms and lung function which the patient attributes directly to these combination inhalers are likely to further enhance adherence.[35] Increased adherence improves asthma outcomes, with regular ICS intake reducing the airway inflammation and the long-lasting bronchodilator effects of the LABA improving asthma symptoms, without risking the adverse effects of either LABA or ICS over-use.[35,36]
- In a systematic review that compared the clinical effectiveness of the ICS fluticasone propionate and budesonide and the LABAs eformoterol fumarate and salmeterol xinafoate administered alone or in combination, single-inhaler combination regimens (budesonide/formoterol and fluticasone/salmeterol) were frequently more effective in improving all treatment outcomes than either monotherapy alone.[37]

Safety advantage of combination ICS/LABA inhalers

When ICS and LABA are prescribed in separate inhalers, there is a risk patients may stop taking the ICS, either in error or because they perceive the LABA is more effective than the ICS.[38] A combination ICS/LABA inhaler may reduce asthma mortality by avoiding periods of LABA monotherapy, and increasing the prescription and adherence with ICS in patients with asthma.[39] Moreover, better adherence with ICS is expected to improve the underlying airways inflammation, which will reduce the chance of a potentially life-threatening attack of asthma.

Combination ICS/LABA therapy in New Zealand

The two LABAs that are currently available in New Zealand are eformoterol (Oxis, Foradil) and salmeterol (Serevent). LABAs are not licensed for use in children aged younger than 4 years (salmeterol) and younger than 6 years (eformoterol).

The available combination delivery options include salmeterol with fluticasone (Seretide) and eformoterol with budesonide (Symbicort and Vannair). PHARMAC subsidises each of these products only for patients who have already tried and failed to control their asthma on the single-drug inhalers for a treatment period of at least 3 months. The individual components of the combination inhalers are funded without restriction in New Zealand.

For full prescribing details regarding these treatments, consult the corresponding New Zealand Medsafe data sheets (http://www.medsafe.govt.nz).

Expert commentary on maximising patient outcomes

Jim Reid: The repeat prescription syndrome for asthmatics is alive and well in New Zealand. Patients often request refills of their inhalers by telephone and often a considerable time can pass between formal reviews. There is real danger that patients use only the "blue inhaler" and I have unpublished evidence that approximately 30% of patients prescribed both short-acting β agonists (SABAs) and ICSs do not know the difference between the two – only that "the blue one works" and the "orange or brown one" doesn't.

There are two basic issues with respect to combination therapy:

1. Safety
2. Adherence to therapy

Asthmatics should **never** be prescribed LABAs without ICS. This is in contrast to current knowledge with chronic obstructive pulmonary disease (COPD), where it seems as though it is safe to use them alone.

In asthma, when the ICS and LABA are prescribed separately, there is real danger that one will be taken without the other – the LABA without the ICS or the ICS without the LABA.

It is a big ask to get patients to use three inhalers separately – a preventer, a controller and a reliever – a brown or orange one, a green one, and a blue one. There is good evidence that the simpler the treatment regime the greater the chance that the patient will adhere to it.

Asthma is an episodic disease, and requires regular medical surveillance. The single most important question that the doctor can ask is how many times has it been necessary to

use their blue inhaler. In one NZ study, some patients considered their asthma was under good control even though they were needing their reliever seven or eight times a day.[18] If on review, it is considered asthma is under good control (not needing the reliever more than (say) 3 times a week), then back titrating of both ICS and LABA is indicated. But do it one at a time. With severe asthmatics my practice is to throttle back the ICS first, but not of course discontinue it, and then if all is well to reduce or discontinue the LABA. I follow the same regime with children.

As an opposite, if asthma is not controlled, I add a LABA to a moderate dose of ICS and if control is not achieved I step up the ICS dose.

Major studies on combination LABA/ICS therapy in asthma with independent Commentary by Associate Professor Jim Reid

Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group[40]

Summary: The results of this trial suggested that the addition of eformoterol to budesonide therapy or the use of a higher dose of budesonide may be beneficial in patients who have persistent symptoms of asthma despite inhaled glucocorticoid therapy. The addition of eformoterol to budesonide therapy improved symptoms and lung function without lessening the control of asthma.

Method/Results: Exacerbation rates in 852 adult asthmatics being treated with glucocorticoids were examined in this double-blind, placebo-controlled year-long comparison of low-dose ICS (100 µg budesonide twice daily) with or without concomitant eformoterol (12 µg twice daily), with high-dose ICS (400 µg budesonide twice daily) with or without concomitant eformoterol (12 µg twice daily). The rates of severe and mild exacerbations were reduced by 26% and 40%, respectively, when eformoterol was added to the lower dose of budesonide. The higher dose of budesonide alone reduced the rates of severe (defined as a decrease in the peak flow to >30% below the baseline value on two consecutive days or the need for oral glucocorticoids) and mild exacerbations by 49% and 37%, respectively. The greatest reductions (63% and 62%, respectively), were observed in the patients treated with eformoterol and the higher dose of budesonide. While symptoms of asthma and lung function improved with both eformoterol and the higher dose of budesonide, the improvements with eformoterol were greater.

Comment: This study showed that combination of LABA (eformoterol) and ICS (budesonide) reduced exacerbations in both moderate and severe adult asthmatics. While there was reduction in exacerbations upon both upping the ICS and the addition of LABA, the exacerbation rate was by far the best in the combination with the higher dose of budesonide.

Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies[41]

Summary: The combination of an ICS and LABA appears to be associated with superior adherence compared with ICS alone or both medications in separate inhalers.

Method/Results: This study retrospectively assessed patient asthma medication refill persistence, using medical and pharmacy claims data over 24 months (12-month baseline and 12-month follow-up) from a large managed care organisation. A total of 2511 subjects aged ≥12 years were identified with a claim for asthma: 563 patients receiving FSC (fluticasone propionate and salmeterol combination in a single-inhaler), 224 receiving fluticasone propionate plus salmeterol, 75 receiving fluticasone propionate plus montelukast, 798 receiving fluticasone propionate only, and 776 receiving montelukast only.

Twelve-month baseline asthma medication use and patient demographics were comparable among cohorts. Patients in the FSC cohort obtained significantly more refills compared with the number of fluticasone propionate refills in the other fluticasone propionate-containing cohorts (4.06 for FSC vs 2.35 for fluticasone propionate plus salmeterol, 1.83 for fluticasone propionate plus montelukast, and 2.27 for fluticasone propionate alone) over the 12-month follow-up period. In addition, patients taking FSC had similar refill persistence compared with patients using oral montelukast (4.51).

Comment: Patients are not complete fools. If something works, and they associate it with working, they will continue to use it. That is why SABAs are so popular with asthmatics – they work and the patient obtains fairly immediate gratification. This study demonstrated that patients perceived value from the combination therapy. They would of course have obtained somewhat similar results if they had adhered to individual therapies – but with three inhalers?

Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma[42]

Summary: This trial established that poor adherence to ICS among adults with asthma is correlated with several poor asthma-related outcomes. Less than perfect adherence to ICS appears to account for the majority of asthma-related hospitalisations.

Method/Results: The investigators retrospectively identified 405 adults aged 18–50 years who had asthma and belonged to a large US-based health maintenance organisation between January 1, 1999, and December 31, 2001. Adherence indices, as calculated by medical records and pharmacy claims, revealed an overall adherence to ICS of approximately 50%. Adherence to ICS was significantly and negatively correlated with the number of emergency department visits (correlation coefficient [R] = –0.159), the number of fills of an oral steroid (R = –0.179), and the total days' supply of oral steroid (R = –0.154). After adjusting for potential confounders, including the prescribed amount of ICS, each 25% increase in the proportion of time without ICS medication doubled the rate of asthma-related hospitalisation (relative rate, 2.01; 95% CI, 1.06 to 3.79). A total of 80 asthma-related hospitalisations occurred during the hospital period; an estimated 32 hospitalisations would have occurred were there no gaps in medication use (60% reduction).

Comment: Basically we are at a stage now with asthma (with some exceptions) where if a patient will comply with therapy most asthma can be controlled. If the patient knows about and adheres to the treatment regime, and knows what to do when undergoing an exacerbation (written action plan) the need for hospitalisation should be a rarity. Unfortunately, such is not the case, and patients do not adhere to treatment, especially to ICSs. Adherence to treatment is a complex issue and beyond the scope of this comment, but one important issue is simplicity of therapy. If we can persuade the asthmatic to take their ICS but once a day it would be a great help. If they perceive real benefit from taking it, the more likely that they will comply. The addition of a LABA at the time of taking the ICS does just that – it produces a perception of benefit.

Safety of long-acting β agonists for the treatment of asthma: clearing the air[39]

Summary: This systematic analysis of the available clinical evidence and safety requirements for LABA use concludes that LABA monotherapy significantly increases the risk of asthma-related adverse effects. However, the use of LABAs in combination with ICS significantly reduces asthma hospitalisations and is not associated with life-threatening events and asthma-related deaths. The researchers state that the evidence supports the use of LABAs plus ICS in a single-inhaler device (to increase adherence and eliminate the potential use of LABA monotherapy) for all patients (not only children) with moderate to severe asthma.

Analysis: In response to the serious concerns about the use of LABAs for asthma, this review critically examined the available clinical evidence and the different safety requirements for the use of LABAs, using data from nearly 20 systematic reviews and databases. According to the evidence, LABA monotherapy significantly increases the risk of asthma-related adverse effects, whereas concomitant use of LABAs with ICS significantly reduces asthma hospitalisations and is not associated with life-threatening events and asthma-related deaths. This is particularly the case when concurrent use of LABAs and ICS can be reasonably assured (use of a single-inhaler device). The reviewers note that some of the new US FDA recommendations have caused confusion and do not appear to be fully evidence-based. They add that although the evidence is limited by low statistical power, it supports the use of LABAs plus ICS in a single-inhaler device (to increase adherence and eliminate the potential use of LABA monotherapy) for all patients (not only children) with moderate to severe asthma.

Comment: Reduced exacerbations, reduced hospitalisations, increased safety when ICSs and LABAs are used in combination – is there an argument in using them separately – I think not. There are real savings if asthmatics can be kept out of hospital, and a reduction in exacerbations does just that.

Call for withdrawal of LABA single-therapy inhaler in asthma[43]

Summary: These respiratory specialists recommend that LABAs are banned for use in asthma as single-inhaler products because of the increased mortality risk when they are used without an accompanying ICS.

Review: This commentary on the evidence concerning the risk of LABA monotherapy states that guidelines already recommend against using only LABAs for asthma, but that this will inevitably occur in practice because of poor patient adherence with the separate corticosteroid inhaler.

The article adds that the risk of LABA monotherapy can be avoided by using combination inhalers containing both a β agonist and ICS, which also has the benefit of promoting increased use of ICS than when the two drugs are prescribed in separate inhalers. Use of the combination inhalers has been associated with reductions in asthma mortality reported with LABA monotherapy, note the researchers. They call for the withdrawal of LABAs as single-inhaler therapy, and recommend that LABA use is restricted to being combined with ICS in inhalers for asthma. They point out that this recommendation is evidence-based and reduces the potential risks of LABAs while allowing patients to obtain the major symptomatic benefits of this therapy.

The researchers concede that LABA single-therapy inhalers should be kept on the market for use in COPD, which occurs in about 20% of smokers.

Comment: This paper really summarises what "I am on about". This reviewer would disagree that LABA single-therapy inhalers should be kept on the market for use in COPD. There is danger that they will be used in asthma alone, while some COPD patients have a mixed picture of asthma and COPD. In addition, there is emerging evidence of the benefits of ICSs in moderate and severe COPD.

Long acting beta agonists – where are we at with safety?[44]

Summary: This review of the available clinical evidence concerning the safety of LABA therapy in asthma up until 2006 concludes that LABAs are very useful agents to use when control of asthma cannot be gained with ICS alone with the addition of no more that two puffs of short-acting β-agonists (SABAs) per day. The article advises that LABAs should always be monitored by a doctor especially for the first few weeks of therapy and always be used in conjunction with ICS. LABA monotherapy is not advised for use as a substitute for ICS.

Review: In relation to the higher mortality associated with the LABA salmeterol recorded in 1993 by a UK-based nationwide surveillance study comparing salmeterol with the SABA salbutamol in asthmatic patients who required regular bronchodilator treatment, this review notes that the mortalities were rare and not of statistical significance. Subsequent, similar evidence was obtained from the Salmeterol Multicentre Asthma Research Trial (SMART) study, although increased morbidity was more prevalent among the Afro-American cohort, and the data indicated that the risk is increased among those patients not on ICS. An advisory from Medsafe issued in 1999 acknowledged the occasional reports of deterioration in asthma control, and even respiratory arrest, following the commencement of salmeterol and eformoterol.[45] It also noted that several mechanisms need to be considered to explain such reactions including paradoxical bronchospasm, increased bronchial responsiveness and tolerance, none of which was identified in prospective studies.

This more recent review states that international data point to a decrease in asthma deaths since the introduction of LABAs, perhaps in response to the increased primary use of ICS. At the time that this review was written, the most up-to-date Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (2006)[46] suggested that LABAs were appropriate as monotherapy in COPD; the recently updated GOLD criteria (2010)[47] maintain this position. However, this review advises that the use of LABA monotherapy in COPD should be viewed with caution, in the light of the risks associated with such treatment. The review goes on to say that reports of paradoxical bronchoconstriction in asthmatic patients after salmeterol metered-dose inhalation have not been observed with use of a powder device, which suggests a reaction to the propellant.

The article concludes that LABAs are very useful agents in conjunction with ICS and should be closely monitored by a doctor in the first few weeks of therapy. LABA monotherapy should not be substituted for an ICS.

Comment: This paper was written in 2006. Nothing much has changed, but now after six years is it not time that we eliminated the risk?

Jim Reid's Take-Home Messages

- Never prescribe a long-acting β agonist (LABA) in isolation for an asthmatic – without an inhaled corticosteroid (ICS).
- Review asthmatics regularly, and be prepared to titrate therapy up or down.
- Convert to combination therapy (ICS + LABA) as soon as the three-month requirement by PHARMAC has been satisfied.
- Ensure that any other asthma patients still on separate inhalers after three months are converted to combination therapy.
- Emphasise the importance of adhering to the treatment regime even though initially it may be necessary to use three inhalers separately.
- Check inhaler technique regularly.
- Provide a written action plan so that patients know what to do in an exacerbation, and when to do it.

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