Do adverse respiratory effects of beta$_2$-agonists contribute to asthma morbidity and mortality?

In this article, **Colin Deeney** discusses some controversial issues that have been raised with regards to the regular use of beta$_2$-agonist bronchodilators in the treatment of asthma. (This article appeared in PJ, 12 August 2006, pp193-5)

Short-acting beta$_2$-agonists (SABAs) have been used as first line therapy for the acute relief of bronchoconstriction in asthma for several decades. However, anti-inflammatory therapies are now considered the cornerstone of chronic asthma management.[1,2] Therefore, it is now recommended that unless individual patients are shown to benefit from regular treatment SABAs are used only when required for acute symptoms. Indeed, regular use is usually seen as an indication of poor asthma control and a need for preventive medication. In contrast, long-acting beta$_2$-agonists (LABAs) are recommended for regular use to control persistent breakthrough symptoms. They are only recommended as an adjunct to preventive inhaled corticosteroids and not as monotherapy.

These recommendations, however, fall against a background of concern expressed about the possibility of increased morbidity and mortality with the regular use of beta$_2$-agonists since at least the mid-1960s. Their use first became a concern after a study in England and Wales showed a rise in deaths that occurred with the introduction of isoprenaline. Then, in New Zealand during the 1970s, again a rise in deaths corresponded with an increase in the use of the fenoterol. In both these cases the cause of the increased mortality was attributed to cardiovascular adverse effects, because isoprenaline is a non-selective agonist and fenoterol is a fairly non-selective beta$_2$-agonist. However, a subsequent study[3] raised the suggestion that the increasing use of beta$_2$-agonists per se may actually be contributing to the world-wide increase in morbidity and mortality from asthma.[3]

Concern regarding potential adverse respiratory effects has focused chiefly on tolerance to the effects of the drugs and also the possibility of rebound airway hyperresponsiveness, increased inflammation or the masking of the underlying disease. Most of the evidence, and thus concern has related to SABAs rather than LABAs. Indeed previous reviews and thus guidelines[1,2,4] have found concern regarding the regular use of LABAs unjustified. However, a recent meta-analysis concluded that regular use of not only SABAs but also LABAs has adverse effects on respiratory function.[5] The review suggested that use of all beta$_2$-agonists may be associated with poorer disease control in patients with asthma compared with no use at all.[5] Furthermore, an interim analysis of another recent study found a higher number of asthma-related deaths or life-threatening events among patients treated with salmeterol compared with placebo.[6]

This was then followed by the results of another study that found a numerical but not statistically significant greater incidence of asthma-related deaths in patients with asthma treated with salmeterol compared with regular salbutamol.[7] Indeed in the US, the Food and Drug Administration Pulmonary-Allergy Drugs Advisory Committee has recently requested that products containing either salmeterol or formoterol should have a "black box" warning of the risk of asthma exacerbations and the possibility of an increased risk of respiratory-related deaths. Yet this contrasts with the findings of another recent large population based study[8] that found that SABAs, but not LABAs, were associated with a small but significant increase in mortality. The authors suggested this increase in mortality had several explanations only one of which may be a direct adverse effect. Therefore the suggestion that beta$_2$-agonists may be contributing to an increase in morbidity and mortality from asthma is controversial.

There are of course pharmacological and physicochemical differences between SABAs and LABAs. Formoterol is a full agonist and is thought to owe the long duration of action to moderate lipophilicity causing it to be retained in the lipid cell membrane and released slowly.[9] Salmeterol is a partial agonist that binds almost irreversibly with the beta$_2$-adrenoceptor.[10] Its long duration of action may also be due to its lipophilicity resulting in a slow onset but prolonged receptor activation.[9] Alternatively, it has been suggested that salmeterol's duration of activity may be due to the fact that it binds not only to the active site of the receptor but also to another site — the "exosite". This anchors it to the receptor and provides for repetitive active-site binding events.[11] However, the relevance of these differences in relation to adverse effects is uncertain. The question therefore still arises: are the adverse respiratory effects associated with SABAs also associated with formoterol and salmeterol?

Tolerance

Studies have shown that regular use of both SABAs and LABAs leads to tolerance to both peak effect and duration of bronchodilation with subsequent doses.[12–15] In addition, there is evidence that tolerance develops to the use of SABAs following regular use of LABAs. However, other studies have found tolerance to LABAs to be of little clinical significance.[16–22] It has been suggested that this is because these studies only involved patients with mild to moderate asthma who were not actually experiencing bronchospasm during investigation.[23] This suggestion followed two studies that found tolerance to SABAs in patients actually experiencing bronchospasm following regular terbutaline[24] and formoterol,[23] the latter despite regular inhaled corticosteroids. Therefore, there is concern regarding tolerance to beta$_2$-agonist bronchoprotective properties, ie, the ability to prevent bronchospasm induced by bronchoconstrictor stimuli. This may be a concern should the patient have an acute attack. Indeed, several studies have shown that regular use of SABAs leads to loss of bronchoprotection to artificial and natural stimuli such as methacholine,[3,15,24–27] histamine,[28,29] adenosine 5'-monophosphate (AMP),[15] propranolol,[28] allergens[26,30] and exercise.[31] There is also evidence that regular use of LABAs is associated with loss of bronchoprotection against methacholine,[32–40] allergen challenge[41] and exercise.[42–44] Furthermore, this tolerance has been shown not to be preventable by inhaled cosrticosteroids.[36,37,43]

It is thought that tolerance to the bronchodilatory and bronchoprotective effects of beta$_2$-agonists is associated with reductions in both the density of peripheral beta$_2$-adrenoceptors (down-regulation) and the binding affinity of the receptors (desensitisation).[45] As regards tolerance to bronchoprotective effects, bronchoconstrictive stimuli can act either directly on smooth muscles or indirectly by stimulating the release of mediators from mast cells. Tolerance could, therefore, theoretically be due to a down-regulation of beta$_2$-receptors on either

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airway smooth muscle or mast cells, or both.

It appears that with SABAs, tolerance to the bronchoprotective effects against bronchoconstriction induced by AMP is of a greater magnitude than tolerance to the bronchoprotective against direct stimulation by methacholine.[25] Since AMP produces bronchoconstriction through the release of mediators from mast cells and methacholine directly constricts airway smooth muscle, this differential has been interpreted as selective beta$_2$-adrenoceptor refractoriness at the mucosal mast cellular level.[25]

With LABAs the situation is somewhat different. There is tolerance to both the bronchoprotective effects against methacholine[23] and AMP[46] with formoterol. However, in contrast to both formoterol and SABAs, regular salmeterol treatment has been shown to lead to loss of bronchoprotection to direct stimulation by methacholine but not to AMP.[47] This implies that mast cell beta$_2$-adrenoceptor downregulation is not the mechanism for tolerance to the bronchoprotection with regular salmeterol therapy. However other studies[42–44] have found a loss of salmeterol bronchoprotection to the exercise, which is also considered an indirect cause of bronchoconstriction. Although this may be attributable to a difference in the mechanisms of bronchoconstriction between AMP and exercise, it also adds to a lack of clarity. Furthermore, in mild asthma, single doses of salmeterol do not appear to protect more against AMP than against methacholine challenge.[38] Therefore, at present it is impossible to conclude that loss of bronchoprotection by salmeterol is due to an entirely different reason than SABAs.

Polymorphism

In recent years attention has been drawn to beta$_2$-adrenoceptor polymorphism. For example, the Glu-27 variant is completely resistant to agonist-promoted down-regulation compared with the Gln-27 variant[48,49] and is associated with lower bronchial hyperreactivity.[50] There is also an association between elevated levels of IgE and the Gln-27 variant.[51] *In vitro* studies have also shown that, compared with the Arg-16 form, the Gly-16 variant of the beta$_2$-adrenoceptor is more down-regulated by beta$_2$-agonist exposure. Indeed the Gly-16 variant has been associated with nocturnal asthma[52] and an increased requirement for oral corticosteroids.[53] However in one study, it was patients with the Arg-16 variant who experienced a decline in morning peak flow with regular beta$_2$-agonist use.[54] The sharpest decreases occurred in the four-week period after beta$_2$-agonists had been discontinued. Patients with this Arg-16 variant who were in the "as required" group experienced no adverse effects. Patients with the Gly-16 variant did not experience such an effect. Furthermore, in another study, subjects of all genotypes demonstrated poorer control of asthma when treated with regular fenoterol compared with "as required" therapy.[55] However, those patients with the Gly-16 variant did not have the increase in bronchial responsiveness experienced with the other genotypes. So although beta$_2$-adrenoceptor polymorphisms may alter the response to the use of beta$_2$-agonists the clinical effects and associations noted have been contradictory and warrant further study.

Rebound airway hyper-responsiveness

It has also been suggested that regular use of beta$_2$-agonists may actually enhance bronchial contractile sensitivity, referred to as rebound bronchial hyper-responsiveness or hyper-reactivity. In other words, there is an increase in bronchoconstrictive response upon challenge with regular use of the drugs. The hyper-responsiveness appears to be transient and occurs after the bronchodilator effect of the beta$_2$-agonist has waned. Given the fact that beta$_2$-agonists are used to alleviate bronchoconstriction, this could result in a cycle of increased bronchoconstriction upon challenge followed by increased use of the bronchodilator and again increased hyper-responsiveness. Put more crudely, the more often a beta$_2$-agonist is used the more it may appear to the user that it is needed. Again, although there is some evidence of this occurring with LABAs,[32,56] there is more evidence of it occurring with SABAs.[26–30,57] One possible mechanism for this increased sensitivity is cross talk between bronchodilating and bronchoprotective pathways (the G protein-coupled receptor pathway). This could then lead to enhanced signalling. This has been found in a study in mice,[58] with the researchers suggesting that it may be due to an adaptive programme that promotes a defined equilibrium so as to maintain bronchomotor tone or reactivity within a specific range.

Research has also suggested that chirality may be relevant. It appears that bronchodilation is almost exclusively the result of stimulation by the R-enantiomer, with the S-enantiomer making little therapeutic contribution (salbutamol and formoterol have been studied). In contrast the S-enantiomer of the racemic beta$_2$-agonist appears to be responsible for rebound bronchial hyperresponsiveness.[59–61] Furthermore, studies with salbutamol have also found that the racemate undergoes stereoselective sulphatisation by sulfotransferases mainly in the gut and liver, so that unwanted S-enantiomer remains for a longer time in the body and reaches higher plasma levels than R-enantiomer.[62,63] Therefore, the use of the R-enantiomer alone may reduce the likelihood of pulmonary adverse effects while maintaining clinical efficacy.

Increased Inflammation

Bronchoalveolar lavages, sputum samples and biopsies after regular treatment with SABAs have shown an increase in a number of inflammatory indicators, as found in both the early and late asthmatic response. For example, after as little as 10 days there is an increase in allergen-induced late asthmatic response indicators such as mast cell tryptase,[64] oesinophils,[64–68] sputum eosinophilic cationic protein[66] and chemokine (CXCL8/interleukin-8) production.[69] The situation regarding LABAs is again somewhat more complicated. A number of *in vitro* and *in vivo* studies have suggested that LABAs may actually have an anti-inflammatory effect.[17,70–72] However, although others have failed to show any anti- or pro-inflammatory effect,[73–76] one study found that there was an increase in markers of inflammation with salmeterol.[77] This increase was reduced with triamcinolone.[77]

It has been suggested that there is an additional benefit in using this combination of a LABA along with inhaled corticosteroids rather than either of the two drugs separately. For example, a number of clinical studies have shown that addition of a LABA to an inhaled corticosteroid gives a better outcome than increasing the dose of the corticosteroids in terms of a number of end points, including exacerbation rate.[17,73,78,79] In addition, an *in vitro* study has shown that beta$_2$-adrenoceptor down-regulation can be reversed by exposure to corticosteroids.[80] Other *in vitro* studies have shown that combining a LABA and corticosteroid, when compared with either agent alone, reduces cytokine release from inflammatory cells,[81] inhibits the release of cytokine-induced intercellular adhesion molecule-1 (ICAM-1)[79] and inhibits vascular cell adhesion molecule-1 (VCAM-1) upregulation.[79] The combination also inhibits granulocyte-macrophage colony stimulating factor (GM-CSF) production of human fibroblasts which should in turn inhibit the migration of inflammatory cells into pulmonary tissue of asthmatic airways.[79] Indeed, another study[82] has attributed this anti-inflammatory effect of the combination to the R-enantiomer, again with the S-enantiomer having a deleterious effect by reversing this. This study found similar results for both salbutamol and formoterol.

Effects of chronic bronchodilation

It has also been suggested that regular use of LABAs may mask the underlying disease and delay awareness of worsening asthma and airway inflammation. For example, the prolonged bronchodilator effect of LABAs could make such clinical markers as symptom scores, nocturnal awakenings, lung function tests and beta$_2$-agonist reliever use less useful in detecting worsening inflammation. Studies have shown that the effects of even a single dose of LABAs can mask the clinical effects of airway inflammatory-cell influx following challenge.[83–85] It has also been found that the frequency of emergency events is greater during treatment with LABAs than with no bronchodilator at all, despite concomitant use of inhaled corticosteroids.[86] This suggests the possibility that LABAs may mask a major exacerbation and delay intervention.

Another suggestion has been that chronic bronchodilation could lead to an increased load. That is, lead to an excessive allergen, microbe or irritant deposition from the atmos-

phere and as a result increase, for example, acute inflammation or bronchial hypereactivity.[87] However, there is little evidence to support or negate this possibility.

Hyperventilation and hypocapnia

One pharmacologically predictable, yet rarely mentioned, effect of beta-adrenoceptor stimulation is increased ventilation, ie, an increase in both the rate and volume of breathing measured as the minute volume. Perhaps it has not been considered of clinical significance. However, recently there has been an increased awareness of the fact that there is dysfunctional breathing including hyperventilation associated with asthma.[88] Patients with asthma hyperventilate during an asthma attack.[89,90] Furthermore, hyperventilation makes asthma worse. For example, acute voluntary hyperventilation causes bronchoconstriction in people with asthma.[91] Hyperventilation reduces arterial carbon dioxide ($PaCO_2$) levels leading to below normal levels known as hypocapnia. Indeed people with asthma have been found to have hypocapnia even when their symptoms are mild.[92,93] Hypocapnia is known to cause and potentiate bronchoconstriction[94–96] and is associated with rebound bronchial hyper-responsiveness.[93] Carbon dioxide levels can drop particularly low at the time of an asthma attack.[90,97] Therefore it has been hypothesised that hypocapnia contributes to,[92,95,98,99] or indeed may actually cause (see www.buteyko.info), airway obstruction and bronchospasm in asthma. Furthermore, hypocapnia has been shown to attenuate hypoxic pulmonary vasoconstriction, worsen intrapulmonary shunt and systemic oxygenation in dogs.[100] Therefore, one adverse effect of both SABAs and LABAs could be to exacerbate asthma by increasing ventilation causing or exacerbating hyperventilation and hypocapnia. Indeed hypocapnia is a known effect of $beta_2$-agonists.[101]

Conclusion

As I stated in the introduction, previous reviews and guidelines[1,2,4] have found concern regarding the regular use of $beta_2$-agonists, and LABAs, in particular, unjustified. However, the results of one recent meta-analysis[5] found that most of the studies in the past that have concluded that $beta_2$-agonists are beneficial were actually funded or sponsored by pharmaceutical companies that might have had a conflict of interest. In other words, they stand to gain financially from $beta_2$-agonist use. Most of the studies not funded or sponsored by pharmaceutical companies found no benefit. This is a controversial statement. Perhaps more importantly, the authors also pointed out that "to date no randomised trials have demonstrated a reduction in disease progression or in mortality with the use of $beta_2$-agonists". This concurs with the opinion of others that "bronchodilator drugs improve lung function in the short term, but their effects are limited to the duration of action of the drug within the airway. Cessation of treatment leads to a rapid decline in lung function, indicating that these protective effects are due to functional antagonism of bronchoconstriction and are not related to any fundamental effect on airway structure."[102] In other words, although $beta_2$-agonists and LABAs, in particular, control symptoms, their use is of limited value in terms of chronic disease outcomes.

In conclusion, although this article is hardly the last word on potential respiratory adverse effects with $beta_2$-gonists, it summarises some of the concerns that have been raised. Indeed, there appears to be sufficient evidence to advise the use of SABAs on an as-needed basis only, as current guidelines recommend. As regards LABAs, there is some evidence that they may augment inhaled corticosteroids in the control and management of asthma, as is recommended in current guidelines. However, there is still some concern with their use. There is some evidence of tolerance to their bronchodilator and bronchoprotective effects. There is also tolerance to SABAs after the use of LABAs. Concern has also been expressed that, by artificially maintaining bronchodilation for a long period, LABAs could mask the underlying disease progress and increase load. Therefore $beta_2$-agonists should continue to be used with caution.

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