Airway Subsensitivity with Long-Acting $\beta_2$-Agonists
Is There Cause for Concern?

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Summary

Regular treatment with both long- and short-acting $\beta_2$-agonists results in tolerance to their bronchoprotective effects, although the relevance of this phenomenon in terms of long term asthma control remains unclear. However, there appears to be no appreciable difference between the 2 long-acting $\beta_2$-agonists, salmeterol and formoterol, in their propensity to induce $\beta_2$-adrenoceptor downregulation and subsensitivity.

The degree of subsensitivity appears to be somewhat greater with indirect stimuli such as exercise and allergen challenge, compared with direct stimuli such as histamine and methacholine. This loss of functional antagonism with long-acting $\beta_2$-agonist therapy is partial and is not prevented by concomitant inhaled corticosteroid therapy. However, the protective effects of inhaled corticosteroids on their own appear to be additive to those of long-acting $\beta_2$-agonists when both drugs are concomitantly administered in the long term.

The subsensitivity to bronchoprotection may be of clinical relevance in terms of patients who are inadvertently exposed to indirect bronchoconstrictor stimuli such as allergens or exercise, suggesting that long-acting $\beta_2$-agonists should not be taken on a regular basis for this particular indication.

There is a greater tendency for bronchodilator subsensitivity to develop with longer-acting, than with shorter-acting $\beta_2$-agonists, and this may reflect the longer duration of $\beta_2$-adrenoceptor occupancy and consequent downregulation. As with the bronchoprotective effects of long-acting $\beta_2$-agonists, the development of bronchodilator subsensitivity is only partial and occurs regardless of whether patients are taking concomitant inhaled corticosteroid therapy. The long-term bronchodilator action of the long-acting $\beta_2$-agonist itself is maintained within the twice daily administration interval. However, subsensitivity occurs in relation to a blunted response to repeated doses of short-acting $\beta_2$-agonists, as in the setting of an acute asthma attack. There is considerable inter-individual variability in the propensity for downregulation and subsensitivity, which is determined by genetic polymorphism of the $\beta_2$-adrenoceptor.

Current international asthma management guidelines suggest that long-acting $\beta_2$-agonists should only be used on a regular basis in patients who are inadequately controlled on inhaled corticosteroid therapy, so the addition of long-acting $\beta_2$-agonist therapy is an alternative to using higher doses of inhaled corticosteroids. There are, however, concerns that regular long-acting $\beta_2$-agonists might result in mask-
\[ \beta_2\]-agonists have been widely used over the past 3 decades and have an established place as first-line bronchodilator therapy in the management of patients with asthma. However, the role of \( \beta_2\)-agonists in international asthma management guidelines has undergone continual reappraisal for a number of reasons. There have been ongoing concerns, particularly regarding the regular use of short-acting \( \beta_2\)-agonists and possible adverse effects on asthmatic disease control and bronchial hyper-reactivity.\(^{[1-4]} \) This has coincided with an greater awareness of the importance of underlying inflammation in the pathogenesis of asthma and has resulted in the increased use of inhaled corticosteroids for preventive therapy.\(^{[5,6]} \)

Thus, a rational treatment protocol evolved, whereby regular inhaled corticosteroids were used to suppress the inflammatory cascade, such that short-acting \( \beta_2\)-agonists should only be used as reliever therapy for bronchospasm on an as-required basis. Indeed the requirement for reliever therapy with short-acting \( \beta_2\)-agonists is considered to be a sensitive marker as to whether or not airways inflammation has been adequately suppressed by inhaled corticosteroids.

Against this background, the long-acting \( \beta_2\)-agonists, salmeterol and formoterol, have become available over the past 5 years and have been increasingly used in most developed countries. Initially, long-acting \( \beta_2\)-agonists tended to be reserved for patients who required short-acting \( \beta_2\)-agonists on a regular basis, despite a high dosage of inhaled corticosteroids (above 1000 \( \mu \)g/day). Because of their duration of action, long-acting \( \beta_2\)-agonists tend to be used on a regular basis, once or twice daily, in an attempt to improve daytime and nighttime control of symptoms.

The use of regular long-acting \( \beta_2\)-agonists has continued to evolve with an increasing awareness of the dose-response relationships for inhaled corticosteroids, in terms of the latter’s relative airways and systemic effects above 1000 \( \mu \)g/day.\(^{[7]} \) Therefore, for many patients with asthma, modern management guidelines now suggest adding a regular long-acting \( \beta_2\)-agonist to an inhaled corticosteroid at corticosteroid dosages lower than 1000 \( \mu \)g/day, as an alternative to increasing the corticosteroid dosage.

Whilst this strategy may prevent possible long term systemic adverse effects of high-dosage inhaled corticosteroids, there may also be problems associated with the use of regular long-acting \( \beta_2\)-agonists. Concerns have been raised that improvements in symptom control and peak expiratory flow rate (PEFR) associated with the use of regular long-acting \( \beta_2\)-agonists might mask uncontrolled underlying inflammation that is inadequately suppressed by inhaled corticosteroids. In addition, there is also a worry that patients’ compliance with their inhaled corticosteroid therapy may decline because they can immediately perceive improvements resulting from initiation of treatment with a long-acting \( \beta_2\)-agonist.

Regular use of \( \beta_2\)-agonists causes \( \beta_2\)-adrenoceptor downregulation and associated subsensitivity.\(^{[8]} \) This subsensitivity, or tachyphylaxis, is known to occur with both short- and long-acting \( \beta_2\)-agonists when used on a regular basis. However, it is conceivable that with regular use of long-acting \( \beta_2\)-agonists, prolonged receptor occupancy over a 24-