Long-acting beta$_2$-adrenoreceptor agonists: salmeterol and formoterol

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The long-acting beta$_2$-adrenoreceptor agonists salmeterol and formoterol, given by inhalation, have a bronchodilating effect lasting for at least 12 hours after a single administration. They complement but not substitute inhaled glucocorticoids in the management of asthma and are also used in the management of chronic obstructive pulmonary disease (COPD).

Introduction

Inhaled short-acting beta$_2$-adrenoreceptor agonists have been used for over 40 years in the treatment of asthma. They are considered as first-line therapy for asthma treatment as they provide rapid bronchodilation and protect against stimuli, such as exercise, allergen, or pollutants that cause bronchoconstriction in asthmatic patients.[1] Salmeterol and formoterol are the first two drugs of a new generation of long-acting beta$_2$-adrenoreceptor agonists given by inhalation with bronchodilating effects lasting for at least 12 hours after a single administration. Both of these drugs have become important complements in the regular management of asthmatic patients who are not sufficiently controlled with inhaled glucocorticoids.[2] Also, regular use of a long-acting beta$_2$-adrenoreceptor agonist improves health status in patients with COPD.[3]

Pharmacological differences

Formoterol and salmeterol have similar pharmacological properties: both are highly selective and potent beta$_2$-adrenoreceptor agonists, with relaxant effects on bronchial smooth muscle *in vitro*. However, some significant pharmacological differences between these drugs have been documented *in vitro* and in patients, as shown in Table 1.[2]

Formoterol has a more rapid onset of action than salmeterol, which may make formoterol suitable for symptom relief as well as symptom prevention in the management of asthma. However, the long-term safety of regular treatment with formoterol at higher doses per day than those recommended by the manufacturer has not been established.[5] Therefore, it is imperative to instruct the patient that formoterol should ONLY be used every 12 hours.

Dose comparison

In most adult patients treated with inhaled long-acting beta$_2$-adrenoreceptor agonists, symptoms will be satisfactorily controlled on 50mcg salmeterol twice daily or 12mcg formoterol twice daily. If these drugs are used in higher doses, attention must be paid to side effects.[7] Studies in adult patients with mild-to-moderate asthma showed that salmeterol 50mcg[8], and formoterol, 12 and 24mcg[9], administered from a metered-dose inhaler were safe and had a low degree of cardiac effects. However, studies[10,11] comparing the cardiovascular effects of formoterol and salmeterol administered at the recommended single doses in patients suffering from chronic obstructive pulmonary disease (COPD) with preexisting mild-to-moderate arrhythmias and hypoxaemia suggested that formoterol 24mcg induces a statistically significant increase in heart rate when compared with placebo and formoterol 12mcg, and salmeterol 50mcg. Additionally both formoterol 12mcg and salmeterol 50mcg have a significantly greater effect than placebo, but there were no differences between these two treatments.

Beta$_2$-adrenoreceptor agonists can decrease plasma potassium levels by stimulation of beta$_2$-adrenoreceptors in the

Table 1. Pharmacological differences between formoterol and salmeterol[2,4,5,6]

	Salmeterol	Formoterol
Onset of action	15-30 minutes	1-3 minutes
Duration	Up to 12 hours	Up to 12 hours
Efficacy	Partial agonist	Full agonist (higher efficacy)
Peak bronchodilation	1-2 hours	30 minutes
Drop in serum potassium	Drop in serum K^+	Possible larger drop in serum K^+
Finger tremor	Pronounced	More pronounced
Heart rate and Q-Tc intervals	No significant difference compared to formoterol	No significant difference compared to salmeterol

liver and skeletal muscle. With the 24mcg dose, but not the 12mcg dose, formoterol produces a statistically significant decrease in serum potassium levels in patients with mild-to-moderate asthma. Also, salmeterol in doses up to a 50mcg was not found to modify the serum potassium level, whereas there was a trend toward a decrease in potassium with a 100mcg dose in patients with mild-to-moderate asthma.

Moreover, doses higher than 12mcg in the case of formoterol and 50mcg in the case of salmeterol do not improve FEV_1 further, thus not showing dose-dependent effects of the drugs on this measurement. Therefore, formoterol produces little additional effect in dosages beyond 12mcg twice daily. Salmeterol produces little additional effect in dosages beyond 50mcg twice daily but does produce more side effects.[7] Therefore, the recommended single dose of salmeterol 50mcg and formoterol 12mcg allows a relatively higher safety margin than salmeterol 100mcg and formoterol 24mcg.[10]

Formoterol and salmeterol as add-on therapy in asthma

Studies have shown that adding a long-acting $beta_2$-adrenoreceptor agonist to patients who are not controlled with inhaled glucocorticoids only, statistically significantly decreases exacerbations and hospitalizations in these patients.[13] These studies have also shown that in patients with persistent asthma combining salmeterol or formoterol with a median of 400mcg of beclomethasone or equivalent results in greater improvement from baseline in FEV_1, in symptom-free days and in the daytime use of rescue $beta_2$-adrenoreceptor agonists than prescribing a higher dose of inhaled glucocorticoids only (median of 800 to 1000mcg per day of beclomethasone or equivalent).[14] However, long acting inhaled $beta_2$–adrenoreceptor agonists should only be prescribed as add on therapy in asthmatic patients who are already taking inhaled glucocorticoids.[15] It is important that formoterol or salmeterol should not be used as monotherapy in asthma as these medications do not appear to influence the airway inflammation in asthma.[16] Results from the Salmeterol-Multi Centre Asthma Research Trial (SMART) showed that patients who did not use inhaled glucocorticoids with salmeterol had a higher incidence of asthma-related adverse events than patients who did use inhaled corticosteroids with salmeterol.[1,17-19]

When administered as an aerosol by a metered-dose inhaler or when inhaled as a powder via a dry-powder inhaler, formoterol and salmeterol have the property of retaining a bronchodilatory effect for up to 12 hours, which accounts for their use in patients with nocturnal asthma. Moreover, the long duration of action permits for a twice daily treatment frequency, rather than every 4 hours as with short-acting $beta_2$-ardrenoreceptor agonists thereby encouraging patient adherence to treatment.[2]

Table 2. Criteria for introduction of add-on therapy[15]

1. Before prescribing add-on therapy, practitioners should assess adherence, inhaler technique and attempt to eliminate trigger factors.
2. The first choice as add-on therapy to inhaled steroids in adults and children (5-12 years) is an inhaled long-acting $beta_2$-adrenoreceptor agonist (formoterol or salmeterol).
3. If there is no response to treatment the drug should be discontinued.

Table 3. Advantages of formoterol and salmeterol as add-on therapy[16]

1. Improve symptom scores
2. Decrease nocturnal asthma
3. Improve lung function
4. Decrease the use of short-acting inhaled $beta_2$-adrenoreceptor agonists
5. Reduce the number of exacerbations
6. Achieve clinical control of asthma in more patients, more rapidly, and at a lower dose of inhaled glucocorticosteroids than when inhaled glucocorticosteroids are given alone.
7. May be used to prevent exercise-induced bronchospasm since they provide a longer protection than rapid-acting inhaled $beta_2$-adrenoreceptor agonists.

Advantages of long-acting beta$_2$-adrenoreceptor agonists

Addition of long-acting inhaled beta$_2$-adrenoreceptor agonists to a daily regimen of inhaled glucocorticoids in asthmatic patients has various advantages, as listed in Table 3.

Long-acting beta$_2$-adrenoreceptor agonists in COPD

In COPD, airflow is obstructed during expiration, thus causing dyspnoea. In contrast to asthma, the airflow obstruction is not reversible and usually progresses over time.[20] The major goals of bronchodilator therapy in COPD are to prevent exacerbation, achieve symptom relief, improve pulmonary functions and, in the long term, enhance the quality of life.[19] Results of systematic reviews or large randomized clinical trials indicate that long-acting beta$_2$-adrenoreceptor agonists in patients suffering from COPD without asthma, statistically significantly reduce airflow obstruction and symptoms. However, the clinical significance is unclear and careful consideration of the costs and benefits of long-acting beta$_2$-adrenoreceptor agonists in patients without asthma is needed before using these drugs in COPD.[21]

Practice Points

- Patients with asthma given salmeterol or formoterol should always initially be prescribed an inhaled glucocorticoids.[17]
- Patients should be monitored closely during early treatment.[17]
- Long-acting beta$_2$-adrenoreceptor agonists should ONLY be used every 12 hours.
- A dose of 50mcg salmeterol twice daily is comparable to 12mcg formoterol twice daily.
- Inhaler technique should always be reviewed prior to making any changes in the patient's treatment.
- Different brands of long-acting inhaled beta$_2$-adrenoreceptor agonists have different licensing properties. Some of these preparations are not licensed for certain age groups. It is imperative to always refer to specific manufacture recommendations prior to prescribing long-acting inhaled beta$_2$-adrenoreceptor agonists.

Delivery

Inhaled long-acting beta$_2$-adrenoreceptor agonists may be delivered via a metered dose inhaler or a dry powder inhaler. It is essential that health care professionals proactively engage in instructing patients on inhaler technique. An inhaler should only be prescribed after the patient has received the necessary training and has demonstrated his/her ability to use the device properly. Regular assessment of inhaler technique is imperative as inappropriate technique leads to inadequate delivery resulting in suboptimal control. Information regarding training of inhaler technique may be accessed at www.ginasthma.com.[22]

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