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# Inhaled $\beta_2$ -agonists in asthma management: an evolving story

## Landmark papers in respiratory medicine

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### From the beginning...

Sympathomimetic agents have been known in Chinese medicine for at least 5000 years as a drug to treat disorders of respiratory tract; however, they were introduced to western medicine mainly in the beginning of the 20th century [1].

Adrenaline and isoproterenol were the first to be introduced, although, being unselective  $\beta$ -agonists, they were prone to significant side-effects. Through the years, new formulations and routes of administration of these drugs, namely the inhaled route, were associated with more bronchodilation effect and fewer side-effects than the oral or subcutaneous ones [2]. The discovery by LANDS *et al.* [3] that  $\beta$ -receptors can be subdivided in  $\beta_1$ , located in the heart and intestinal smooth muscle, and  $\beta_2$ , located in bronchial, vascular and uterine smooth muscle, directed the research to new selective  $\beta_2$ -agonists drugs.

In the 1960s, fenoterol, salbutamol and terbutaline were developed [1, 2]. These  $\beta_2$ -selective agonists were more tolerable and efficient. Therefore, they were easily accepted, and salbutamol became the most widely used short-acting  $\beta_2$ -agonist (SABA) for the relief of asthma symptoms [1, 2]. However, one major limitation of these drugs was their short duration of action, which

was inadequate for control of nocturnal symptoms and limited their use for maintenance treatment [1]. For these reasons, long-acting  $\beta_2$ -agonists (LABA) were developed in the 1980s.

With duration of action that reached 12 h, formoterol and salmeterol were considered for long-term treatment, particularly among patients who did not achieve control under regular inhaled corticosteroids. The mechanisms for their long duration have been debated, and it seems that different physicochemical properties in contact with the cell membrane and with the  $\beta_2$ -receptor might explain their characteristics. According to ANDERSON *et al.* [4], the lipophilicity of formoterol and salmeterol allows them to enter and be stored in the cell membranes, promoting a depot release of the drug: the “plasmalemma diffusion microkinetic model”. Regarding formoterol, as it is moderately lipophilic, some molecules are kept in the aqueous phase outside the cells and interact immediately with the  $\beta_2$ -receptor, which explains its faster onset of action [1]. The use of SABA in comparison with LABA for maintenance treatment started to be compared both for efficacy and safety.

The Serevent Nationwide Surveillance (SNS) study [5] compared the use of salmeterol (50  $\mu$ g, twice daily) with that of salbutamol (200  $\mu$ g, four times per day) in a large randomised double-blind



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clinical trial in parallel groups over 16 weeks, which recruited asthma patients from general practices throughout UK (3516 general practitioners). This study reported results from more than 25000 patients with asthma and showed that the overall asthma control, assessed by use of oral corticosteroids and need for a relief inhaler, was better with salmeterol than with salbutamol. Similarly, general practitioners' classification of severity significantly decreased more in the salmeterol than in the salbutamol group. Overall, almost 70% of the individuals were already on inhaled corticosteroid maintenance treatment.

Regarding formoterol, the FACET (Formoterol and Corticosteroids Establishing Therapy) study [6] was also a multicentre randomised double-blind clinical trial in parallel groups and compared the association of formoterol to budesonide, at 100- or 400- $\mu$ g dosages, *versus* budesonide alone, at 100- or 400- $\mu$ g dosages. Addition of formoterol to inhaled corticosteroid treatment lead to an improvement of asthma-symptom scores and lung function, and reduced the need for asthma medication, and reduced severe and mild exacerbations; the individuals under the combination of a  $\beta_2$ -agonist and a high dose of inhaled corticosteroids had the greatest reduction. The use of combination treatment has now become one of the cornerstones of asthma management. Nevertheless, some apprehension regarding safety appeared due to the increase in asthma-related mortality during the evolution of  $\beta_2$  agonists.

## Safety of inhaled $\beta_2$ -agonists: controversies regarding a black box

Asthma-related deaths showed two peaks, in the 1950s and 1970s. The mortality increase in the 1950s occurred shortly after the introduction of a high dose of inhaled isoproterenol. This peak subsided after publicity against overuse of this drug and the appearance of selective  $\beta_2$ -agonists [1]. However, a second peak of asthma-related deaths began in the late 1970s, reported by a matched case-control study from New Zealand with 117 patients [7]. In this study, the relative risk of asthma deaths was 1.55 (95% CI 1.04–2.33) among those using fenoterol in a metered-dose inhaler.

Concerns increased about the regular use of SABA for asthma treatment, and several studies started to show an association of chronic use of fenoterol with asthma exacerbations, a significant decline in lung function and an increase in airway hyperresponsiveness [1]. The multiple mechanisms that might have explained these results were nicely summarised by Anne Tattersfield [2]. However, tachyphylaxis resulting in reduced bronchodilator sensitivity to  $\beta$ -agonists

and induced tolerance to their bronchoprotective effect, and dysrhythmias, might be the most likely associated mechanism, particularly if drugs were used at high doses. Recently, there has been an association of  $\beta_2$ -adrenoreceptor polymorphisms with a poor response to  $\beta_2$ -agonists, which might increase the need for higher doses to reach efficacy [1, 2] and therefore be associated with serious adverse effects.

Apprehension over LABA use in maintenance treatment for asthma started soon after their launch, considering the previous history with SABA and the possibility that long-term bronchodilators could mask deteriorating asthma and be associated with severe exacerbations. The SNS study reported an increase of asthma-related deaths in patients treated with salmeterol compared with salbutamol [5]. During the study, 12 deaths occurred due to respiratory and asthma-related causes, 7.1 per 10000 patients in salmeterol group *versus* 2.4 per 10000 patients in the salbutamol group. As the number of events was very small, this difference did not reach statistical significance. These reports increased the discussion in the US Food and Drug Administration (FDA) regarding safety of LABA.

In 2003, a black box warning was added to the drug labels based also in the data from the Salmeterol Multi-Center Asthma Research Trial (SMART) [8]. SMART was a multicentre, randomised, double-blind, parallel-group, placebo-controlled trial of 28 weeks duration involving 26355 asthma patients in which it was compared the usual maintenance treatment for asthma to the association of salmeterol (50  $\mu$ g twice daily) to their usual therapy. Baseline use of inhaled corticosteroids in the population was 47%. This study showed an increase in the respiratory-related and asthma-related deaths in the salmeterol group, particularly in the African-American individuals. In order to assess the risk and benefits of LABA, and to provide the scientific community with a clarification, the FDA began considering results from additional studies.

A large, comprehensive meta-analysis of asthma clinical trials was conducted in 2010 by the FDA and included 110 trials with more than 60000 patients. Despite SMART having an important weight in these results due to its larger sample, the pooled data showed an increase risk of asthma-related events with LABA in comparison with SABA, particularly if the use of inhaled corticosteroids in combination was not mandatory. New safety requirements were created based on these results [9]:

- contraindication of single use of LABA
- step-down treatment with LABA after control is achieved
- in those under control with low and medium doses of inhaled corticosteroids, LABA should not be added
- prefer fixed-dose combinations of LABA and inhaled corticosteroid to increase compliance

Furthermore, the FDA requested new large prospective trials to evaluate the safety of combining LABA with inhaled corticosteroids. These studies have recently been released for salmeterol (AUSTRI) [10] and formoterol [11], though results seem reassuring, with no significantly higher risk of serious asthma-related events. Given the fact that these are scarce events, perhaps only a future systematic review and meta-analysis will provide a final answer regarding safety.

## Looking in to the future: ultra-long $\beta_2$ -agonists

Recently, new ultra-long  $\beta_2$ -agonists with higher potency and selectivity to  $\beta_2$ -receptors, like vilanterol, olodaterol, indacaterol and abediterol [12, 13], with 24-h treatment duration and rapid onset of bronchodilation have been studied. Of these, only vilanterol, in association with inhaled corticosteroids, has been approved for treatment

of asthma [12]. The once-a-day posology might increase adherence in long-term treatment of asthma. However, superiority to twice-a-day LABA still cannot be concluded with the currently available evidence [12]. In addition, no serious adverse effects have been observed, although the follow-up periods of the trials are short. Due to the high selectivity to  $\beta_2$ -receptors of these drugs, it is not expected for them to have greater adverse cardiovascular effects than LABA. Conversely, this selectivity may potentially be correlated with a greater loss of adrenoreceptors but this has not been associated with functional desensitisation [14]. Moreover, with an increasing human life expectancy, these new drugs should be shown to be safe and efficacious in an older population that may have a higher rate of cardiovascular comorbidities and use of multiple medications.

The use of ultra-long  $\beta_2$ -agonists is increasing, prescribed in monotherapy for chronic obstructive pulmonary disease (COPD), and frequently asthma-COPD overlap syndrome. New data are emerging every day and will continue this story in the future.

### Conflict of interest

None declared.

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