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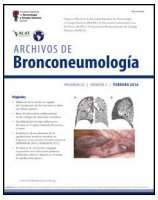

Editorial

β_2-agonists in asthma: the strange case of Dr Jekyll and Mr Hyde

β_2-agonistas en asma: el extraño caso del Dr Jekyll y Mr Hyde

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Bronchial asthma is a major public health problem, affecting more than 300 million people worldwide, and its prevalence is steadily rising in most developed countries.[1] Current strategies in the management of patients with asthma are focused on achieving disease control. ®$_2$-agonists play an important role in this regard. These drugs are classified according to the duration of the bronchodilator effect, and short-acting ®$_2$-agonists (SABA) are distinguished from long-acting ®$_2$-agonists (LABA) when the effect lasts for 12 h, or even longer in the case of ultra-LABAs.

Despite the enormous benefit of ®2-agonists in the treatment of asthma (Dr. Jekyll), major alarms concerning their use have been raised since they were first introduced (Mr. Hyde). Indeed, an increase in mortality associated with the use of SABA[2] had already been reported as early as the 1960s, and in 1979, a peak of 4.1/100,000 asthma deaths per year in a population aged between 5 and 34 years was observed in New Zealand.[3] While this increase in mortality was associated with overuse of these drugs, their use in monotherapy also appears to be a determinant factor. Currently, concerns have shifted to LABA, the use which was already questioned in 1993, when a trend towards an increase in mortality in asthmatic patients treated with salmeterol was observed.[4] This trend was confirmed by the results of the SMART study, which found that mortality was 4.4 times higher in patients receiving salmeterol compared to placebo.[5] This increase in mortality associated with LABA was also reported in 2006 in a meta-analysis that included results from 19 randomized placebo-controlled studies.[6] In this context, the FDA analyzed approximately 61,000 cases and concluded that the risk of an asthma-related serious adverse event e.g. death, intubation, or hospital admission was 2.8 times higher per 1,000 patients treated with LABA compared to those who did not receive these products.[7]

Given the questions raised by these results and the observation that these adverse effects did not appear to occur if the LABA was administered concomitantly with inhaled corticosteroids, the FDA demanded that the 4 large companies producing LABA (AstraZeneca, GlaxoSmithKline, Merck, and Novartis) conduct 5 studies, 4 in adolescents/adults and 1 in a pediatric population, comparing patients randomized to receive inhaled corticosteroids + LABA versus inhaled corticosteroids in monotherapy at a fixed dose during 6 months. The individual results of these studies,[8–11] together with the pooled analysis of all outcomes,[12] seem to indicate that the administration of LABA in asthmatic patients is safe provided they are given in combination with inhaled corticosteroids and at doses not exceeding 50 μg/12 h salmeterol or 9 μg/12 h formoterol.

However, it is becoming increasing common to see LABA escalation in clinical practice simultaneously with the escalation of doses of inhaled corticosteroids, without taking into account these safety limits and the inherent risk of overdosing these drugs. Moreover, few benefits in terms of efficacy have been reported with these dose increases. However, questions are being raised as to whether these dose increases might predispose to a greater number of exacerbations. While Wofe et al.[13] did not find a greater number of exacerbations in patients treated with formoterol 24 μg/12 h compared to patients treated with lower doses, Mann et al.[14] reported that doses of 24 μg/day were associated with a 4.5% risk of developing a serious asthma exacerbation, whereas the risk was only 2% if doses of 12 μg/day were used. LABAs are currently used in patients with moderate or severe asthma. However, the latest update of the GINA guidelines[1] states that the combination of budesonide/formoterol can be used on-demand in patients with mild asthma. This recommendation is based on the SYGMA

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1[15] and SYGMA 2[16] studies, sponsored by Astra-Zeneca, which reported that patients with mild asthma receiving budesonide 200 μg + formoterol 6 μg on-demand had fewer exacerbations than patients receiving terbutaline on-demand. Although this treatment schedule was not inferior in terms of preventing exacerbations, when compared with budesonide 200 demand had fewer exacerbations g twice a day + terbutaline on-demand it was inferior in terms of asthma control. These results have recently been reproduced in a real-world study (also sponsored by Astra-Zeneca) without the limitations imposed by clinical trials.[17] Extreme caution is needed when choosing this therapeutic option, and to avoid awakening Mr. Hyde the dose should probably not exceed 18 demand had fewer exacerbations g/day.

The reason why ®$_2$-adrenergic receptors have this double personality is unknown, although the data seem to point to their action on ®$_2$-adrenergic receptors in the bronchial smooth muscle. In this respect, genetic variants, such as the 9 different ®$_2$-adrenergic receptor polymorphisms identified, could explain this effect. Variable expression after the stimulation of protein receptors such as EPAC or arrestins could also be the cause. Either way, our efforts should be directed at ensuring, above all, that these drugs are never administered in monotherapy; in fact, they should be contraindicated in patients with asthma unless they are administered in conjunction with inhaled corticosteroids.[18] We must also raise awareness among all medical professionals treating patients with asthma that the established safe doses must not be exceeded. The combinations of LABA and inhaled corticosteroids that are so helpful in avoiding monotherapy may be dangerous if they are progressively escalated without taking into account the maximum safe dose for LABA.

Robert Louis Stevenson published *The Strange Case of Dr Jekyll and Mr Hyde* in 1886. A few years before that, in 1860, Sir Henry Hyde Salter opened the door to the treatment of asthma with ®-agonists when he observed that bronchial smooth muscle contraction was the main cause of obstruction in these patients.[19] Any relationship between both Mr. Hydes is purely coincidental.

Conflict of interests

Xavier Muñoz has received honoraria as a speaker, scientific advisor, and participant in clinical studies from (in alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Mundifarma, Novartis, and Teva.

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