

## Bronchodilator use in asthma: the art of prescribing bronchodilators correctly, taking advantage of their differences and reducing risks

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The history of the development of bronchodilators of the  $\beta_2$ -agonist group, which evolved concomitantly with the understanding of the physiopathology of asthma, is an excellent example of how scientific thinking develops, based on hypotheses that comprise partial truths and are progressively filtered in order to improve the understanding of something that should occur, but sometimes does not. Failures are discovered from these continuous observations, and we evolve toward a new generation of intervention, in an attempt to determine the ideal treatment. Formoterol, a long-acting  $\beta_2$ -agonist (LA  $\beta_2$ ), is analyzed in this issue of the Brazilian Journal of Pulmonology regarding its efficacy in reversing methacholine-induced bronchospasm. The study compared formoterol with a short-acting  $\beta_2$ -agonist (SA  $\beta_2$ ), fenoterol, demonstrating the equivalence of action of formoterol with one of the drugs considered the gold standard for reversibility of severe bronchospasm, the short-acting bronchodilators. The study population was selected from patients who sought diagnostic clarification of their respiratory symptoms at the pulmonary function laboratory. The patients who tested positive on the provocation test were included in the study.<sup>(1)</sup>

The study protocol allows us to clearly observe that the initial speed of action of the LA  $\beta_2$  is equivalent to that of the SA  $\beta_2$ , demonstrating a truth that has come to stay: formoterol, in addition to being devised as long-acting, also has the property we seek, which is to promptly relieve severe bronchospasm, and presents a great advantage over salmeterol. This allows us to advocate its use in severe bronchospasm.

This study leads to another quite relevant issue that has been debated in the literature and was the object of a perspectives article in the December, 2005 issue of the New England Journal of Medicine, written by Prof. Dr. Fernando D. Martinez (invited to participate in the next Brazilian Congress of

SBPT - Fortaleza, 2006).<sup>(2)</sup> In that article, the use of long-acting bronchodilators is discussed, together with the review on the principal clinical studies that led the FDA to include an alert, in the directions for use, to the users of salmeterol, in July of 2005, announcing a small, albeit significant, increase in adverse events associated with asthma, and characterized as imminent risk or complications or death, present in a safety study recently completed in the USA. Prof. Martinez questions the consequences of this alert for the treatment of asthma.

This study, the Salmeterol Multi-center Asthma Research Trial (SMART), initiated by GSK in July of 1996, was a 28-week safety study comparing salmeterol to placebo in the treatment of asthma, in addition to routine maintenance treatment. The primary outcome was to observe the deaths and serious adverse events related to asthma that endangered the life of the patients (intubation and mechanical ventilation). The study had the intention of including 60,000 patients but was interrupted by the sponsor after the interim analysis, which was carried out with the inclusion of approximately 26,000 patients. They demonstrated a 4.4-times higher relative risk of death in the salmeterol group in relation to the placebo group. Another randomized study, carried out in the United Kingdom and published in 1993, comparing the use of salmeterol with that of salbutamol and involving 25,000 patients, revealed that there were fewer dropouts among the patients who received salmeterol than among those who received salbutamol (2.91% versus 3.79%;  $\chi^2 = 13.6$ ,  $p = 0.0002$ ). Mortality was a little higher, although not significantly so, in the salmeterol group. The use of more than two units of rescue bronchodilator (in addition to the maintenance dose) presented significant association with the occurrence of serious adverse events related to asthma.<sup>(3)</sup>

Unfortunately, none of the two studies was planned to test the hypothesis of salmeterol being safe when accompanied by the use of inhaled corticosteroid, although LA  $\beta_2$ s have been used as adjuvant therapy

to inhaled corticosteroid. The patients were randomized with no control of the use and dose of the inhaled corticosteroid during the clinical trial. Therefore, this issue has yet to be clarified.

Reviewing the comments of Prof. Martinez, we are brought back to very interesting occurrences of the end of the last century. In the beginning of the 1990s, a study by Sears et al.<sup>(4)</sup> provoked a great debate in the literature when, through a randomized clinical trial, it was demonstrated that the regular use of an SA  $\beta_2$  four times a day was worse for the asthma patients than the use of an SA  $\beta_2$  when necessary, in relation to the control of the disease. Therefore, they questioned whether the regular use of this drug could be the cause of uncontrolled asthma.<sup>(4)</sup> A retrospective, epidemiological, population-based, nested case-control study<sup>(5)</sup> involving 12,301 asthma patients residing in Saskatchewan, Canada, demonstrated that the risk of death by asthma was not related to the regular use or even increased use of an SA  $\beta_2$  but to the lack of use of the inhaled corticosteroid as maintenance treatment. In addition, either because the disease was uncontrolled or because it was untreated, there was excessive use of the SA  $\beta_2$ .

Therefore, when studies demonstrating the superiority of the combination of an LA  $\beta_2$  in relation to the increased dose of the inhaled corticosteroid (in order to obtain the control of asthma) began to appear,<sup>(6)</sup> this concept appeared to be in conflict. The FACET study,<sup>(7)</sup> which compared the addition of an LA  $\beta_2$ , in low (200 mcg) or high (800 mcg) doses, to a placebo, suggested that the high doses of inhaled corticosteroid were associated with less frequent exacerbations, and that the use of an LA  $\beta_2$  was associated with more symptom-free episodes. Other clinical trials followed, proving the efficacy of combining an inhaled corticosteroid with an LA  $\beta_2$  in controlling of asthma,<sup>(8)</sup> as well as discussing strategies to improve this control.<sup>(9)</sup>

However, what worries us is the fact that some patients do not manage to achieve good control of their asthma. Do they constitute a special group of corticosteroid-resistant patients? Are they responsive to other anti-inflammatories? Do they present low compliance with maintenance treatment? Or is there any other condition that causes their inadequate response to  $\beta$ -agonists? The fact is that, for patients with more severe asthma, when it is not possible to control the symptoms, it remains doubtful as to whether they present an increased risk of complications or even of fatal episodes when using the

maintenance therapy. One thing is certain: inhaled corticosteroids are indisputably the best maintenance treatment for asthma, and, when the effectiveness of a  $\beta_2$ -agonist in reversing severe bronchospasm is presented in this issue of the Brazilian Journal of Pulmonology, it is indispensable to reflect upon the advantages and risks related to the use of bronchodilators, and remember that they must always be combined with the anti-inflammatory treatment of asthma.

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#### Potential Conflict of Interest

The author participated as an investigator in the following international multicenter studies: OPTIMA (1998, Astra-Zeneca); STAY (2000, Astra-Zeneca); and GOAL (2000, Glaxo Smith Kline).

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