



## Editorial

M<sub>2</sub>–β<sub>2</sub> Interaction: A Basis for Combined Bronchodilator Treatment<sup>☆</sup>Interacción M<sub>2</sub>–β<sub>2</sub>: bases para el tratamiento broncodilatador combinadoJosé Luis López-Campos<sup>a,b</sup><sup>a</sup> Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Sevilla, Spain<sup>b</sup> Centro de investigación en red de enfermedades respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

Since the introduction of the first short-acting bronchodilators until the present day, bronchodilator treatment has undergone remarkable advances, with the appearance of new more potent, longer-acting molecules with a better safety profile. This growth in bronchodilator drugs has significantly improved the treatment of obstructive airways diseases, most notably chronic obstructive pulmonary disease (COPD), in which bronchodilation forms the basis of pharmacological therapy.

New long-acting β<sub>2</sub>-adrenergic receptor agonists (LABA) have improved pharmacodynamic parameters, increasing their potency and efficacy.<sup>1</sup> Similarly, the new long-acting muscarinic antagonists (LAMA) also show improvements in their pharmacodynamic profile, with longer duration and more rapid onset of action.<sup>2</sup>

Due to the good clinical results obtained with both families of bronchodilator drugs, the clinical effect that combining two drugs from different groups could have in COPD patients has recently begun to be considered. In this respect, various clinical trials have provided evidence on the effects of using a LABA and a LAMA together.<sup>3–5</sup> These studies have found a functional improvement resulting from their additive action, as well as a clinical impact with improvements in chronic symptoms but less impact on exacerbations.<sup>6,7</sup>

**Description of the Problem**

Although available evidence supports the use of combined bronchodilator treatment in COPD, there are still some unknowns. In this respect, a close review of the literature may reveal two phenomena that require explanation.

The first stems from combination trials evaluating the functional effect of adding a twice daily LABA to a once daily LAMA (tiotropium).<sup>3,5</sup> These studies similarly describe a very illustrative graph that shows the resulting functional improvement after the addition of the first and second dose of twice daily LABA in patients on tiotropium treatment. However, attention must be drawn to the fact that the second dose of LABA, the dose administered in

the evening, achieves smaller functional improvements than those achieved with the morning dose.

This phenomenon may have several explanations. On one hand, the smaller effect of tiotropium 12 h after the onset of action means that the onset of bronchodilation after the second dose of LABA occurs in a different part of the tiotropium action curve. Nevertheless, although this is true, the bronchodilator impact is more minor even if we take into account this decline in the action of tiotropium.<sup>8</sup>

Another possible explanation could be that the LABA acts differently according to the time of day at which it is administered. In this respect, the existence of a circadian rhythm that influences airway calibre has been described. This circadian rhythm causes the calibre of the airways to become smaller during the night, regardless of the state of sleep or wakefulness.<sup>9</sup> To establish the importance of this phenomenon, various studies have been conducted on the efficacy of bronchodilators according to the time of day at which they are administered. Although detailed analysis of their results is beyond the scope of this editorial, most studies did not find major differences between administering a long-acting bronchodilator in the morning or at night, when given separately.<sup>10,11</sup> However, if we study the joint action of two bronchodilators, a once daily LAMA (tiotropium) and twice daily LABA, we come across an interesting finding. A recent study explored the clinical efficacy of the combination of tiotropium and formoterol, in order to study different regimens according to the time of administration of both drugs (morning or evening) and the number of doses in the case of formoterol (1 or 2 doses daily), so five treatment groups were established.<sup>12</sup> In this study, both treatment groups that received formoterol every 12 h plus tiotropium (one group in the morning and the other in the evening) obtained better efficacy in lung function, symptoms and use of rescue medication than the other groups. However, patients with nighttime symptoms obtained a greater benefit in dyspnoea and use of rescue medication if the tiotropium was administered at night together with the formoterol instead of in the morning.<sup>12</sup> This finding had not been described previously, and suggests that the joint action of both bronchodilators is more effective when the administration of the two drugs is closer, which constitutes the second phenomenon that requires explanation.

In order to understand why this functional and clinical improvement occurs with the joint administration of a LABA and a LAMA, we must briefly recall the mechanism of action of bronchodilators.

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## Interaction Between Adrenergic and Cholinergic Receptors

The mechanism of action of the  $\beta_2$  agonists is known and has been recently reviewed.<sup>13</sup> Briefly, the stimulation of these receptors causes activation of G proteins coupled to the  $\beta_2$  receptor, which in turn regulate the action of an adenylate cyclase. This enzyme mediates the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). cAMP regulates the expression of several cellular proteins, among which are the calcium channel, which in turn permits relaxation of the bronchial muscles. Therefore, adenylate cyclase and intracellular cAMP levels play a crucial role in the mechanism of action of the  $\beta_2$  receptors.

There are currently five known types of muscarinic receptors, termed  $M_1$ – $M_5$ .<sup>14</sup> Of these,  $M_1$ – $M_3$  are expressed in the human respiratory tract. Specifically, airway smooth muscle contains a mixed population of  $M_2$  and  $M_3$  receptors. The main bronchodilator effect derived from their inhibition is related with the  $M_3$  receptors, which through G proteins stimulate a phospholipase that in turn promotes the influx of calcium into the cell.<sup>15</sup> However, despite the clear role of the  $M_3$  receptors in muscle contraction, the number of  $M_3$  receptors in the airways is much lower than the  $M_2$  receptors, with a ratio of 4:1.<sup>16</sup>

The role of the  $M_2$  receptor in the action of the LAMAs has not been sufficiently considered until now. However, the function of the  $M_2$  receptors is key for understanding the interaction with the  $\beta_2$  adrenergic receptors in the airways. It is known that the  $M_2$  receptors inhibit (via the G proteins) the generation and accumulation of cAMP in the cell, which is the mechanism of action of the  $\beta_2$  receptor. Thus, stimulation of an  $M_2$  receptor would inhibit the action of the  $\beta_2$  receptor. Although the exact site of interaction where this inhibition occurs is unknown, the relationship between both receptors contributes jointly to the contraction of the bronchial smooth muscle.<sup>17</sup>

## $M_2$ – $\beta_2$ Interaction: Clinical Implications

From the above, it appears that it would be plausible to suggest that the effect of stimulating the  $\beta_2$  receptor would be greater during  $M_2$  receptor inhibition. To understand the clinical implications of this suggestion, we must remember the tiotropium pharmacodynamic studies. It is well known that tiotropium exerts its bronchodilatory action by inhibiting the  $M_3$  receptors. However, it is equally certain that it also inhibits the  $M_2$  receptors, only that this  $M_2$  inhibition is transient, with a half life of 3.6 h.<sup>8</sup> Thus,  $M_2$  receptor inhibition and the subsequent release of  $\beta_2$  last barely a few hours, so if we want to take advantage of the potential benefits of this  $M_2$ – $\beta_2$  interaction, it follows that both drugs must be administered at the same time, in order for the  $M_2$  inhibition to unblock the  $\beta_2$  receptor and allow it to have greater action on being stimulated. This would explain the smaller effect of the second dose in the LABA–LAMA combination studies,<sup>3,5</sup> as it lacks this interaction in the second administration, or the greater clinical effect when the formoterol and tiotropium doses are given simultaneously in the study by Terzano et al.<sup>12</sup>

If this hypothesis is true, it would be advisable to use a LABA together with a LAMA to be able to take advantage of the  $M_2$ – $\beta_2$  interaction. Thus, if once daily bronchodilators are administered, it would be reasonable to recommend their simultaneous administration at the same time of the day, instead of one in the morning and the other at night. On the contrary, if a twice daily LABA is used, it would be reasonable to recommend the administration of a twice daily LAMA. At present there are two twice daily (salmeterol, formoterol) and one once daily LABAs (indacaterol) available. Only one once daily LAMA has been available to date (tiotropium), although new LAMA molecules have recently been approved with

an administration profile every 12 h (aclidinium<sup>18</sup>) and every 24 h (glycopyrronium<sup>19</sup>). Clinical trials exploring the clinical relevance of this interaction on combining once or twice daily bronchodilators are therefore required.

## Conclusions

In recent years, we have been witnessing an expansion in the development of bronchodilator drugs towards more potent, longer-lasting molecules with a better safety profile. Knowledge of the mechanisms of action of both bronchodilator families, LABA and LAMA, provides us with information that helps us to understand the interaction between both, with a significant role between the  $M_2$  and  $\beta_2$  receptors. Understanding this receptor interaction is crucial for suggesting the optimal form of administration of these drugs, so that the best clinical benefits can be obtained for patients. Future clinical studies must ascertain the clinical importance of this  $M_2$ – $\beta_2$  interaction in specific clinical contexts.

## Conflicts of Interests

The author has received fees for giving lectures, scientific advice, participation in clinical studies and writing articles for (alphabetical order): Ammirall, AstraZeneca, Bayer, Boehringer Ingelheim, Cantabria Pharma, Chiesi, Esteve, Faes, Ferrer, GlaxoSmithKline, MSD, Novartis and Pfizer.

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