



Editorial

Ultra-LAMA, Ultra-LABA, Ultra-Inhaled Steroids? The Future has Landed[☆]

Ultra-LAMA, ultra-LABA, ultra-cortis? El futuro ya está aquí

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We humans tend to believe that the world has always existed in the form in which we know it. History is fine as an object of study, but we rarely make the effort to really situate ourselves in the past. If we ask most pulmonologists who have started or finished their training this century about the origins of inhaled treatment for obstructive lung disease, we might be surprised to find how little they know. But it is difficult to evaluate current developments without taking account of the past.

In fact, inhaled therapies, especially those involving acetylcholine receptor antagonists, have been used for centuries. As early as the 1600s the Hindu system of Ayurvedic medicine prescribed the smoking of alkaloid-rich plants with anticholinergic effects, such as *Atropa belladonna* and *Datura stramonium*, for the treatment of asthma.^{1,2} With the opening-up of the trade routes with India in the nineteenth century, these plants were dried and smoked by British patients to relieve their dyspnea. And in the middle of the twentieth century, classical medicine still prescribed atropine or stramonium-rich cigarettes. However, atropine is a tertiary ammonium that is readily absorbed by the blood; it crosses the blood-brain barrier and has significant adverse effects, and so its clinical utility is limited. More than two thousand years ago, the Chinese used epinephrine extracted from the plant *Ephedra equisetina*, but this substance has low selectivity for β receptors and the duration of its effect is short.³ Inhaled isoprenaline, introduced in the middle of the twentieth century, is a highly potent drug and remains the benchmark against which new β -agonists are compared.³

To understand the pharmacology of inhaled treatments for obstructive respiratory diseases, it is necessary to clarify certain concepts concerning the innervation of the airways, given its effect on the decision to apply bronchodilator treatments, and also concerning the inflammatory capacity of the bronchial mucosa, given its effect on the decision to apply anti-inflammatory treatments. Let us look briefly at these two issues.

Airway tone is maintained primarily through the control exerted by the vagal parasympathetic fibers which maintain a degree of reversible bronchoconstriction as a result of the tone of the airway

smooth muscle.⁴ The pre-ganglionic parasympathetic fibers establish cholinergic synapses with the post-ganglionic parasympathetic fibers located predominantly in the larger airways. One might think that bronchodilator treatments act only on the larger airways, but in fact the post-ganglionic fibers innervate the entire system and nervous stimuli reach the whole of the airway.⁵ Cholinergic parasympathetic fibers and non-adrenergic non-cholinergic fibers regulate airway smooth muscle tone, airway caliber, the airway glands and microvasculature. The airway smooth muscle, however, does not receive direct sympathetic innervation, but contains β -adrenergic receptors; there is also evidence that the parasympathetic fibers receive orders from the sympathetic system.

The binding of acetylcholine to the M_1 receptors in the nerve ganglia stimulates its release from post-ganglionic endings which in turn bind to the M_3 receptors of the airway smooth muscle and submucosal glands, causing bronchoconstriction and increased bronchial secretion. In the ganglia, however, acetylcholine also binds to M_2 receptors, causing a decrease in its production. From a therapeutic point of view it is interesting to note that colinergic receptors can be found in almost of the lung cells (including the airway, vessel smooth, and endothelial cells). In humans, M_1 receptors are mainly located in the peripheric airways and alveolar walls whilst the M_2 and M_3 are predominantly located in the larger airways.^{6–10} Blocking M_1 and M_3 receptors reduces or reverses bronchoconstriction, but M_2 receptor blockade attenuates the decrease in acetylcholine production (that is, it favors its release) thus decreasing the bronchodilator effect of the muscarinic antagonist. The ideal anticholinergic, then, has a high affinity for M_1 and M_3 and low affinity for M_2 .

For their part, the sympathetic fibers from the spinal cord form synapses in paravertebral ganglion chains whose post-ganglionic fibers release norepinephrine in mucous glands and blood vessels but not in the airway smooth muscle.^{11,12} There are, however, adrenergic receptors in the whole of the lung. Of the three types of β -receptor, the most frequent in the lung is β_2 , which accounts for 70% of the total. The β_2 receptor density increases as bronchial subdivision progresses, and is therefore higher in small caliber airways than in larger ones.^{13,14} β_2 receptors are also expressed in many pro-inflammatory cells such as neutrophils, eosinophils, mast cells, and macrophages. β_1 receptors, on the other hand, are found only in the alveoli and the mucous glands.

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This, then, is the histophysiological background to the introduction of the first bronchodilators – the anticholinergic ipratropium bromide and the β -agonists salbutamol, terbutaline and procaterol. Fifty years ago, inhaled therapy consisted of the repeated daytime use of these bronchodilators, whose effect lasted between 4 and 6 h. Research conducted since then has aimed to achieve a lasting bronchodilator effect, introducing the LABA (long-acting β -agonists) formoterol and salmeterol with effects lasting 12 h.

The first ultra-long acting drug marketed was tiotropium bromide, an anticholinergic. Tiotropium bromide is the gold standard against which the various drugs developed since then have been compared. Curiously, it is termed a LAMA (long-acting muscarinic antagonist) though its effect lasts 24 h.¹⁵ Tiotropium binds equally to M_1 , M_2 , and M_3 receptors (that is, it shows the same affinity) but rapidly dissociates from M_2 receptors, so in practice it is quite selective for the M_1 and M_3 receptors and in fact comes close to being the ideal antagonist.¹⁵ Its slow release of M_1 and M_3 receptors is responsible for its lasting effect.¹⁵

Tiotropium has demonstrated improved trough FEV₁ compared with placebo¹⁶; it reduces dyspnea, improves quality of life, reduces exacerbations and hospitalizations due to COPD, improves exercise capacity and inspiratory capacity, and reduces the consumption of other inhaled medication such as β -agonists and inhaled corticosteroids (IC).^{17–19} The “Uplift” study showed that tiotropium was unable to modify the progressive decline in patients’ lung function,²⁰ but it should be noted that the bronchodilator effect of the drug was associated with improvements in lung function, in COPD patients concomitantly with IC+LABA.²¹ However, a subsequent study found that in patients receiving tiotropium for the first time the decline in FEV₁ was lower in those treated with placebo (42 ml/year vs 53 ml/year for tiotropium).¹⁷ The recent POET study showed that compared with the LABA salmeterol, tiotropium reduced both exacerbations and hospitalizations.²² Initially marketed exclusively for COPD, currently the drug is starting to be used also in patients with poorly controlled asthma.²³

The therapeutic success of tiotropium bromide, which has been included in all recent and current guidelines as a first-line drug for the treatment of patients with persistent COPD, encouraged researchers to investigate other similar drugs. Other currently available ultra-LAMA include glycopyrrolate bromide, aclidinium bromide and umeclidinium bromide.

It is not yet clear whether these new drugs are really LAMA or ultra-LAMA, since their prolonged bronchodilator effect may be due to the increase in dose. A recent study has developed a pharmacokinetic model designed and validated from empirical results obtained with a drug in the marketing process that evidenced that at the same total daily dose in once-daily and twice-daily regimens, the trough FEV₁ response to the twice-daily regimen was higher.²⁴ The peak bronchodilator effect was slightly higher with single-dose administration, and 24-h bronchodilation, assessed by the area under the curve of the FEV₁ values, was virtually the same with the two regimens.

Glycopyrrolate’s dissociation half-life from M_3 receptors is shorter than that of tiotropium or aclidinium,²⁵ and in bronchial preparations “in vitro” its effect does not seem to be as long-lasting as that of tiotropium.²⁶ Clinical studies, however, have shown that its rapid bronchodilating effect is maintained over 24 h. Verkindre et al.²⁷ observed that doses of 50 and 100 μ g of glycopyrrolate both showed a greater bronchodilator effect than tiotropium within 5 min, 2 h and 4 h of administration. This suggests that the binding and dissociation kinetics of the M_3 receptor is only one aspect of the drug’s pharmacological effect. A randomized 26-week long placebo-controlled study in moderate to severe COPD²⁸ showed that the bronchodilator effect of 50 μ g of glycopyrrolate administered once daily lasted 24 h and was maintained over time (mean FEV₁ was 108 ml higher in the treated group than the placebo group

at 12 weeks); the drug reduced the risk of first severe exacerbation by 31%, decreased consumption of rescue medication, and improved dyspnea and quality of life. Regarding its safety profile, glycopyrrolate was well tolerated and there were few drug class side effects. Doses of 100 μ g have also proved safe, probably due to glycopyrrolate’s greater selectivity for M_3 than for M_2 receptors.

“In vitro” studies have shown that aclidinium, like glycopyrrolate, has good selectivity for M_3 receptors and less selectivity for M_2 , thus meeting the main requirement of a LAMA. “In vitro” aclidinium offers faster action than tiotropium, though the duration of its effect is shorter. The rapid inactivation of the drug by hydrolysis once in the blood gives it an excellent safety profile.²⁹ The problems with aclidinium began when two Phase 3 studies at doses of 200 μ g/day did not show a correlation between the improvement in trough FEV₁ and improvement in quality of life, or any reduction or delay in the onset of severe exacerbations.³⁰ A subsequent Phase 2 study using a dose of 400 μ g twice daily showed a similar effect to tiotropium.³¹ The advantage of aclidinium is the improvement in nocturnal symptoms, at doses of both 200 and 400 μ g administered twice daily.³²

Finally, although still in the very early stages of development, umeclidinium bromide appears to show a bronchodilator effect similar to tiotropium when administered in a single daily dose. Doses ranging between 62.5 and 1000 μ g have been well tolerated.^{30,33}

Ultra-LABA form the other major group of bronchodilators. The only one currently marketed is indacaterol, although research into others such as olodaterol and vilanterol is at an advanced stage. Indacaterol is a highly lipophilic drug which, unusually, is retained in the lipid rafts of the plasma membrane, an area particularly rich in β receptors. This means that these receptors are repeatedly stimulated by a drug that is retained for a long period in the cell membrane, achieving an effect that lasts 24 h.³⁴ Indacaterol has high intrinsic activity (73%) and its bronchodilator effect appears very quickly, within five minutes of administration.³⁵ A recent meta-analysis by Rodrigo and Heffen³⁶ presented evidence of the advantages of indacaterol over existing LABA and showed that the drug has a bronchodilator effect similar to that of tiotropium. In spite of its greater efficacy it has no drug class side effect. Only a mild self-limited cough that does not require withdrawal of the drug appearing immediately after inhalation in 15%–20% of cases³⁶ has been reported. Furthermore, indacaterol does not counteract the bronchorelaxant effect of salbutamol (unlike salmeterol³⁷; nor does it seem to cause tachyphylaxis,³⁸ possibly because of its high selectivity for β_2 receptors. Its minimum effective dose is 75 μ g (this is the dose marketed in the US) while in Europe it is presented in doses of 150 and 300 μ g.

Olodaterol is a potent β_2 receptor agonist with an intrinsic activity of 88%. This ultra-LABA binds moderately to lipid rafts although its dissociation half-life is about 18 h. Furthermore, it has a two-stage profile of dissociation from β_2 receptors, its slow component having a dissociation half-life of 12 h. These two features explain the fact that the bronchodilator effect lasts 24 h.³⁹ Olodaterol has proven effective at doses of 5 μ g/day in a single dose in patients with COPD (increasing the dose to 10 μ g/day does not seem to provide a greater therapeutic effect,⁴⁰ and in patients with asthma.⁴¹

Vilanterol trifenate is a β_2 -agonist which has greater intrinsic activity than salmeterol and appears to be more potent than indacaterol. The drug has been studied for both asthma⁴² and COPD. A 28-day study of COPD patients using increasing doses of 3, 6.25, 12.5, 25, and 50 μ g showed an improvement in trough FEV₁ value in all cases⁴³; the drug was well tolerated and there were no undesirable drug class side effects.

Let us now look at the last group of drugs, the inhaled corticosteroids mometasone furoate (MF) and ciclesonide (CIC). MF is a potent topical glucocorticosteroid. “In vitro” studies have shown

that it is extremely effective in inhibiting cytokine production⁴⁴ and is one of the most potent stimulators that have been analyzed for glucocorticoid receptor-mediated transactivation of gene expression, with a high affinity for this receptor.⁴⁵ In the study by Bousquet et al.⁴⁴ 730 patients were randomized to one of four treatment groups: MF dry powder inhaler (100, 200 or 400 µg twice daily) or BUD Turbuhaler® (400 µg bid day), in an international, multicenter, evaluator-blind assessor and active-controlled study over a 12-week period. Variations in FEV₁ showed a statistically significant advantage ($P < .05$) of MF 200 and 400 µg twice daily over BUD Turbuhaler® 400 µg twice daily. The results of Corren et al.⁴⁶ were similar. By specifying a single dose per day, treatment adherence is better and the need for rescue medication is reduced.⁴⁷ In children, a dose exceeding 100 µg/day may compromise the patient's growth.⁴⁸

The second inhaled corticosteroid on the market is a non-halogenated corticosteroid, ciclesonide (CIC). The form administered is a prodrug (and therefore inactive) which has low affinity for the corticoid receptor and becomes an active metabolite after its esterification in the airway (des-ciclesonide, des-CIC). Since des-CIC has the same affinity for the corticosteroid as budesonide or fluticasone, not surprisingly, at equipotent doses it has the same pharmacological effect as fluticasone, mometasone, and budesonide.^{49,50}

Formulated in HFA solution and administered in pressurized devices (MDI) (unlike fluticasone, which is formulated in CFC solutions or dry powder), CIC achieves a lung deposition of 52%.⁵¹ The lower oropharyngeal deposition contributes to reducing local adverse effects such as candidiasis and hoarseness.⁵¹

Once it passes into the blood it binds strongly to plasma proteins and is rapidly metabolized in the liver, so its oral bioavailability is low. This is why the drug presents few systemic adverse effects.^{51,52} In addition, des-CIC does not suppress cortisol even at doses of up to 1280 µg/day, whereas fluticasone propionate and budesonide show a dose-dependent relation to cortisol suppression.^{53–55} In general, CIC has a safety profile comparable to placebo.^{56,57} For some time, the small airways were considered a “silent zone” since they contribute only 10% of the whole airway's resistance. During the past 15 years, however, it has been suggested that inflammation may be even more pronounced in small airways than in larger ones. CIC has also been shown to exert anti-inflammatory effects in the small airways, thus improving their function.⁵⁸ To complete the range of therapeutic possibilities, CIC can significantly reduce the need for oral corticosteroids in patients with severe asthma.⁵⁰

In spite of all these advances, a great deal remains to be done. Combinations of drugs of ultra-long duration are being prepared and evaluated for the many different situations included in the clinical guidelines.⁵⁹ In the past, the only combinations marketed were LABA+IC. Though initially designed only for asthma, following on from the success of step-up therapy depending on disease severity^{60,61} LABA+IC have also been widely applied in COPD since the results of the TORCH study.⁶² With the recent reappraisals of treatment strategy for both asthma²³ and COPD⁶³ other combinations have attracted interest such as the association between β-agonists and anticholinergics and even a triple association of β-agonists, anticholinergics and inhaled corticoids (all of them long-acting). For once, it seems that large groups of “ultras” will be nothing to fear.

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