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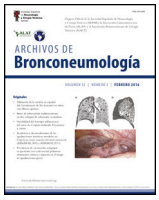

Editorial

Is There Room for Theophylline in COPD?☆

¿Hay un lugar para la teofilina en la EPOC?

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Theophylline, which is inexpensive and widely available, remains one of the most commonly prescribed drugs worldwide for the treatment of asthma and COPD. Data from some studies show that is still being prescribed in 35% of patients with COPD.[1] Despite it being used the world over, in industrialized countries the role of theophylline has changed dramatically in the last decades, and it has become a third-line treatment for poorly-controlled patients.[2,3] This change was due mainly to the introduction of new drugs with more favorable efficacy and safety profiles, such as β2-agonists and inhaled corticosteroids (ICS).

Oral theophylline has been used in COPD for its bronchodilatory properties for more than 70 years. Its mechanism of action is based on the non-selective inhibition of phosphodiesterase and the increase of intracellular cAMP, which relaxes the smooth muscle of the airways. However, this non-selective inhibition of phosphodiesterase causes a wide range of side effects (nausea, vomiting, abdominal pain, metabolic acidosis, seizures, and arrhythmias), which largely restricts the therapeutic range of theophylline (10–20 mg/l); however, to achieve modest clinical effects, relatively high plasma levels over 10 mg/l are needed. We also now know that the bronchodilatory effect of theophylline is weak and, according to an *in vitro* study,[4] the plasma concentration necessary to ensure an optimum effect is 67 mg/l, much higher than that used in clinical practice. For all these reasons, it is not surprising that high-dose theophylline has gradually been replaced by inhaled bronchodilators.

In 2002, Ito et al. described for the first time a new mechanism of action of theophylline. These authors reported a preclinical study in COPD patients, in which oral low-dose theophylline (1–5 mg/l) increased the sensitivity of airway inflammation to the anti-inflammatory effects of ICS. This new anti-inflammatory effect is a result of increased histone deacetylase (HDAC) activity that enhances the anti-inflammatory effect of glucocorticoids by decreasing the expression of proinflammatory genes.[5] Following publication of this study, other groups have confirmed these findings and added to the understanding of the *in vitro* and *ex vivo* mechanisms.[6,7] Some groups have even indirectly correlated some of the molecular changes induced by the combination of theophylline and ICS (increase in hydrogen sulfide [H_2S] concentration) with improved lung function.[8] These data provided a scientific basis to support the pharmacological use of theophylline combined with ICS.

However, few studies are available on the clinical effects of low-dose theophylline *in vivo*, and results are variable. The administration of oral low-dose theophylline in patients with COPD exacerbations significantly reduced HDAC activity in sputum macrophages at 3 months, and could be due to the concomitant administration of oral corticosteroids.[9] In a study in India, COPD patients treated with ICS and low-dose theophylline presented a lower degree of dyspnea and better results in the 6-minute walk test and lung function (pre-bronchodilator FEV1).[10] In contrast, in a clinical trial recently published by our group,[11] COPD patients treated with ICS and low-dose theophylline showed no differences in exacerbation rates compared to the group that received ICS alone. This study was unable to confirm *in vivo* any increase in HDAC activity, the molecular antiinflammatory effect previously observed *in vitro*[5].

In any case, because of its modest bronchodilatory effect, limited and controversial evidence of the oral antiinflammatory effect, and narrow therapeutic range, theophylline is a third-line treatment in current clinical practice guidelines,[12,13] and its use is reserved as a therapeutic option in severely ill patients who do not respond to conventional drugs.

Does this point to the end of theophylline? The availability of the drug and the numerous *in vitro* and *ex vivo* studies that show improvements in the anti-inflammatory efficacy of corticosteroids when combined with low-dose theophylline oblige us, at least, to look for new routes of administration, which might perhaps include the combined administration of the two drugs by inhalation, to confirm if the *in vitro* effects are also reflected in clinically relevant outcomes. Until then, theophylline in COPD will probably continue to be the last option in severely ill patients who fail to respond to previous treatment lines.

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