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EDITORIAL

Theophylline again? Reasons for believing

B.G. Cosio*,# and J.B. Soriano#,¶

So, what is new for theophylline in asthma? Theophylline has been used over the last 70 years for treating patients with asthma. It is well known as a bronchodilator and the current asthma guidelines recommend it as an add-on therapy in noncontrolled asthmatics [1]. More than a decade ago, EVANS *et al.* [2] showed that adding theophylline is equally effective as doubling inhaled corticosteroid (ICS) doses for asthma control. In a recent issue of the *European Respiratory Journal*, SPEARS *et al.* [3] reported significant improvements in both lung function and asthma control score in smoking asthmatics who are treated with a combination of low-dose theophylline and beclomethasone compared with each drug alone. The potential relevance of this small, self-labelled pilot trial is that to our knowledge, it is the first to test an effect of this mechanism in smokers. Worldwide, one in every four asthmatics still smokes; interestingly, the prevalence of smoking in asthmatics mirrors the population prevalence of smoking in that geographic population [4]. Every smoker should quit but anyone with asthma or any other respiratory condition should be offered all options and help to achieve full smoking cessation.

So, what is the point? Something has changed in our scientific knowledge of the mechanism of action of theophylline in recent years. Since ITO *et al.* [5] described *in vitro* a novel anti-inflammatory mechanism of action for theophylline through histone remodelling, efforts have been made to prove that low-dose theophylline can boost the effects of glucocorticoids in chronic airway inflammation *in vivo*. However, most clinicians are reluctant to believe that we are now going to achieve what our medical antecedents were not able to with the same drug. Nevertheless, there is compelling evidence that allows us to revisit the current use of this drug, especially in glucocorticoid-resistant inflammatory processes, such as chronic obstructive pulmonary disease and severe asthma [6].

Theophylline has been used for its bronchodilator properties, which are mediated by phosphodiesterase (PDE) inhibition, resulting in an increase in cAMP, thus relaxing airway smooth muscle. Dose–response studies showed an increasing acute bronchodilator response above plasma concentrations of 10 mg·L^{-1} (55 μM). The problem was that over 20 mg·L^{-1} the side-effects, including a high incidence of nausea and vomiting, abdominal pain, mild metabolic acidosis and other biochemical imbalances, and tachycardia, made it intolerable, which led its therapeutic range to be established at between 10–20 mg·L^{-1}. Therefore, it has been our aim to adjust individual doses to achieve this therapeutic range in our clinical practice. Interestingly, we now know that theophylline is in fact a weak bronchodilator, with an effective concentration giving a 50% response of 1.5×10^{-4} M *in vitro*, which equates to a plasma concentration of 67 mg·L^{-1} assuming 60% protein binding [6]; this is far from the therapeutic range we have been using. Thus, it is not surprising that there is scepticism about the use of theophylline nowadays.

It has been known for some time that theophylline also exerts anti-inflammatory effects in asthma and these have been extensively described; thus, in patients with nocturnal asthma, low-dose theophylline (~5 mg·L^{-1}) reduces the number of eosinophils in bronchial biopsies, bronchoalveolar lavage and induced sputum, whereas in severe asthma, withdrawal of theophylline results in increased numbers of activated CD4+ cells and eosinophils in bronchial biopsies. The classical proposed mechanisms are diverse (PDE inhibition, increased interleukin-10 release, mediator inhibition, inhibition of intracellular calcium release, inhibition of nuclear factor-κB or increased apoptosis) but most of these seem to occur only with higher concentrations of theophylline that are clinically effective (often >20 mg·L^{-1}). ITO *et al.* [5] recently described a novel mechanism of action of theophylline: induction of histone deacetylase (HDAC) activity to decrease inflammatory gene expression. This effect is seen at low concentrations of theophylline (10^{-6}–10^{-5} M) and is lost at higher concentrations (10^{-4} M). The mechanism is not mediated by PDE inhibition because other non-selective and PDE4–PDE3-selective inhibitors do not mimic this action of theophylline. Because induction of HDAC activity is not effective in suppressing inflammatory genes unless it is recruited to the active inflammatory site by activated glucocorticoid receptor, this novel action of theophylline predicts that this drug alone would have weak anti-inflammatory effects at these concentrations. However, it would markedly potentiate the anti-inflammatory actions of glucocorticoids.

SPEARS *et al.* [3] took a rational approach to addressing this potential effect of low-dose theophylline, and investigated the effect of the combination of the glucocorticoid beclomethasone and low-dose theophylline in comparison with each drug alone in smoking asthmatics. It has been previously shown that cigarette smoke inactivates HDAC activity *in vitro* [7]; this could be responsible for a lower steroid responsiveness in asthmatics who smoke [8], so the idea makes sense. But, as usual in all biology systems, the explanation is not so straightforward and the authors did not find a clear effect of

*Dept of Respiratory Medicine, Hospital Universitario Son Dureta, Palma de Mallorca, Spain. #CIBER de Enfermedades Respiratorias. ¶Programme of Epidemiology and Clinical Research, Fundación Caubet-CIMERA Illes Balears, Bunyola, Spain.

CORRESPONDENCE: B.G. Cosio, Dept of Respiratory Medicine, Hospital Universitario Son Dureta, Andrea Doria 55, 07014 Palma de Mallorca, Spain. E-mail: borja.cosio@ssib.es

the combination of glucocorticoid and low-dose theophylline on HDAC activity. As discussed by SPEARS *et al.* [3], there is an obvious methodological issue, owing to the problems of working with sputum samples and the small sample size, making the results inconclusive. Although there are merits to this novel research, the limitations should also be highlighted, some of which have already been discussed by the authors. The study patients seemed to have stepped down their usual ICS dose to a lower dose of beclometasone (*i.e.* from 800 to 200 μg); presumably this was to ensure a sufficient response in order to be able to show synergy with theophylline. It remains to be answered whether theophylline in smokers would still have conferred additivity on top of an optimised dose of ICS, such as 400 μg beclometasone, even though smokers do not show the same dose–response to steroids. The attrition rate during recruitment (see fig. 1 of SPEARS *et al.* [3]) was significant, which raises issues on extrapolation of results. Given the many comparisons tested, correction for multiple comparisons was deemed necessary, which were all included in the *ad hoc* online supplementary material. Finally, the results obtained in this 4-week trial need to be confirmed in a longer term trial. There was, however, a clear synergistic effect of these two drugs on lung function and symptoms, which gives us reason for believing.

If someone had said that acetylsalicylic acid would be used to prevent thrombosis and to maintain the cardiovascular system when it was used in the mid-eighteenth century for its specific effects on fever, pain and inflammation, there would have been a great deal of scepticism. In our era of modern marketing strategies, to promote the use of an old and cheap drug may not be fashionable, but it should be kept in mind given the increasing scientific and clinical evidence available.

STATEMENT OF INTEREST

None declared.

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