

Reproterol: Beta-2-Agonist, Theophylline, or Both?

J. Christian Virchow, Jr.

Department of Pneumology, University Medical Clinic, Freiburg, Germany

In a number of countries reproterol has been used for many years as a bronchodilator in the treatment of asthma. Its mode of action has been attributed to a more or less selective stimulation of β_2 -receptors. Reproterol has gained wide use when it was licensed as a fixed combination therapy with cromoglycate. Until today, the bronchodilator effects of reproterol and the bronchoprotective and anti-inflammatory actions of cromoglycate combined in one inhaler remain the only successful fixed combination of a disease-modifying and symptomatic drug for the treatment of asthma. The practical implications for this were obvious: patients who relied solely on the bronchodilator effects of reproterol for symptom control inadvertently also received a dose of anti-inflammatory medication when taking reproterol/cromoglycate. Theoretically, this seemed especially useful during times of worsening asthma control where the untimely or underdosed usage of anti-inflammatory therapy has been recognized as a major cause of severe asthma exacerbations. In contrast, what has been termed 'rational noncompliance' may have led to a reduction in the administered dose of bronchodilator as well as anti-inflammatory therapy when patients' need for symptomatic asthma control decreased. Although active in many patients, the relative weakness of cromoglycate as an anti-inflammatory agent, however, rarely permitted its use in more severe asthma. Still, this fixed combination, although not potent enough for all asthma, undoubtedly has had advantages in terms of the well-known problems of noncompliance with preventive therapy in asthma. Despite this, until recently, therapy of

asthma with fixed combinations of anti-asthmatic medications were considered problematic for a number of more or less theoretical reasons. This approach has now been strongly questioned by a number of well-designed studies in recent years which have highlighted the advantages of a polypragmatic approach to asthma therapy. Thus, it has been demonstrated that the combination of inhaled corticosteroids with either a long-acting β_2 -agonist [1, 2], theophylline [3, 4], or a leukotriene antagonist [5], have a more favorable effect on pulmonary function and asthma control as compared to an increase in inhaled corticosteroids. Although the issue of compliance has not been addressed by these investigations, they definitely argue in favor of fixed combinations of drugs to treat asthma. Accordingly, new combinations of these drugs are very likely to be introduced in the near future.

In this issue of *Respiration*, Juergens et al. [6] report an interesting observation about the mode of action of the aforementioned reproterol. Using classical pharmacological methods, they were able to demonstrate that reproterol increases the generation of cAMP in isolated peripheral blood monocytes in vitro more effectively than does orciprenaline. In the presence of the highly potent but nonselective β -antagonist, propranolol, the cAMP-generating action of reproterol was inhibited only partially. In addition, LTB₄ generation by LPS-stimulated monocytes in vitro was inhibited by reproterol and theophylline, but not by the sympathomimetic drug orciprenaline. This suggests that the in vitro actions of reproterol, which has long been regarded only in terms of its β_2 -agonist proper-

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J.C. Virchow, Jr.
Department of Pneumology, University Medical Clinic
Hugstetterstrasse 55, D-79106 Freiburg (Germany)
Tel. +49 761 270 3701, Fax +49 761 270 3704
E-Mail virchow@pnm1.ukl.uni-freiburg.de

ties, are at least partially mediated by theophylline-like actions. It remains unclear whether these effects of reproterol are mediated by phosphodiesterase inhibition or other yet unrecognised mechanisms. Obviously, peripheral blood monocytes can only partially reflect the contribution of the many different cells involved in asthmatic inflammation. The *in vivo* relevance of these findings are therefore still unclear. Yet, they allow interesting new speculations about the actions of reproterol but also its combination with cromoglycate. If indeed reproterol has theophylline-like actions, do they translate into clinically relevant effects? A number of anti-inflammatory actions have been reported in the past for theophylline. Although the majority of these have not yet been confirmed, a number of possibly anti-inflammatory properties have been attributed to theophylline such as a reduction in eosinophils [7], CD4+ T lymphocytes [8], CD8+ T lymphocytes [9], the number of IL-4 and IL-5 positive cells *in vivo* [9] as well as a reduction in TNF- α release from alveolar mac-

rophages [10] and an increase in granulocyte apoptosis [11] *in vitro*. Similar actions such as a reduction of eosinophils in the bronchial mucosa and a reduced infiltrate with CD4+ T lymphocytes have also been reported for cromoglycate [12]. Thus, while the results of Juergens et al. [6] suggest that the action of the fixed combination of reproterol and cromoglycate might in fact have been mediated by the triple alliance of a β_2 -agonist, theophylline and cromoglycate, this finding also raises the question how to differentiate the possible anti-inflammatory actions of cromoglycate from those of the theophylline-like moiety of reproterol. As the authors correctly point out, further *in vivo* studies are needed to answer whether these findings bear any *in vivo* relevance. And although the title 'novel aspects of mode of action in asthma' at present appears to be a little too optimistic, the data presented suggest that there is good evidence to believe that the actions of reproterol have been underestimated.

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