Eur Respir J 1999; 14: 249–250
Printed in UK – all rights reserved

European Respiratory Journal
ISSN 0903-1936

EDITORIAL

Long acting inhaled β_2-agonists: anti-inflammatory effects not evident during treatment of day to day asthma

S. Durham

The introduction of long-acting inhaled sympathomimetic β_2-receptor agonists represents an important advance in asthma therapy. Treatment with salmeterol and formoterol provides better control of symptoms and lung function than short-acting β_2-agonists [1, 2] When combined with moderate doses of inhaled glucocorticosteroids, these drugs have been shown to improve symptoms and lung function more effectively than doubling the dose of inhaled corticosteroids [3, 4]. The addition of the long-acting bronchodilator formoterol also reduced the number of asthma exacerbations during a 12-month treatment period, although to a lesser extent than doubling the dose of inhaled corticosteroid [5].

In addition to their bronchodilating properties, beta-sympathomimetic agonists have been shown to have anti-inflammatory properties. However the evidence is based on *in vitro* studies and provocation testing in both animals and humans. There have been concerns that regular use of inhaled β_2-agonists may mask an increase in the underlying airway inflammation occurring in asthma [6, 7]. Furthermore, the long-term use of long-acting inhaled β_2-agonists may result in tolerance to their protective effects against various asthma-provoking stimuli [8–12]. The relevance of anti-inflammatory effects of salmeterol based on *in vitro* studies and challenge models, and the clinical implications considered.

In vitro studies provide evidence for the anti-inflammatory effects of β_2-agonists. Salbutamol is a potent inhibitor of the immunoglobulin (Ig)E-dependent release of histamine from human lung mast cells [13]. Salmeterol inhibited the generation of leukotrienes and prostaglandins, in addition to histamine, from human lung fragments [14]. In a guinea-pig model, salmeterol inhibited allergen-induced protein exudation in both the skin and airways [15]. In patients with allergic asthma, inhaled salbutamol inhibited the rise in plasma histamine associated with immediate allergen-induced bronchoconstriction [16]. Inhaled salmeterol inhibited both the early and late asthmatic responses and associated increases in airway responsiveness following allergen bronchoprovocation [17]. However, inhibition of the late response by salmeterol may be explained, at least in part, by functional antagonism as a consequence of prolonged bronchodilation. Whereas several studies have since confirmed the inhibitory effect of salmeterol on allergen-induced asthma, measurements performed in parallel on inflammatory cell numbers and markers of cell activation in blood and sputum have yielded conflicting results. PIZZICHINI *et al*. [6] and WEERSINK *et al*. [7] found no changes in allergen-induced alterations of eosinophil numbers or eosinophil cationic protein (ECP) levels in blood and/or sputum. They concluded that the functional effects of a single dose of salmeterol may mask the underlying cellular infiltration caused by an inhaled allergen. These results were in contrast to those of PEDERSEN *et al*. [18] who showed that inhibition of early and late asthmatic responses by salmeterol was accompanied by a decrease in both blood eosinophils and serum eosinophil protein concentrations. However, this within-group treatment effect was not significant when compared to the placebo group. A recent study by DENTE *et al*. [19] demonstrated that a single dose of inhaled salmeterol (50 μg) blocked both the early and late asthmatic responses, and inhibited the sputum eosinophilia but not the increases in both sputum and blood ECP concentrations, 24 h after allergen inhalation. It is not clear to what extent these differing results may be explained on the basis of patient selection, dose of salmeterol or the various methodologies employed. Whether the inhibitory effect of salmeterol on early and late responses may be explained by sustained bronchodilation rather than inhibition of allergen-induced inflammatory changes in the airways, remains unresolved.

Inhaled corticosteroids are potent inhibitors of allergen-induced late responses and the associated airway inflammatory changes [20]. Moreover, both inhaled and oral corticosteroids are highly effective in naturally occurring asthma and reduce local inflammatory events as demonstrated by a decrease in markers of T-lymphocyte activation, T-helper-2-type cytokine production and recruitment and activation of eosinophils both in bronchoalveolar lavage and bronchial biopsies [21–24]. In a previous study of salmeterol in naturally occurring asthma, no significant differences in inflammatory cells were detected in bronchial biopsies before and after treatment compared with placebo treatment [25], although the results may have been confounded by the prior treatment of patients with inhaled corticosteroids.

In the study by ROBERTS *et al*. [26] reported in this issue of the Journal, the effects of a six-week treatment regime with salmeterol 50 μg twice daily was compared with placebo in a double-blind placebo-controlled trial. The patients studied had moderately severe asthma as reflected by peak flow variability of ~35% with moderately severely increased airway methacoline responsiveness. Clinical improvement was shown by a 14% increase in morning peak expiratory flow rates and a marked reduction in airway methacholine responsiveness, both of which were significant between the groups. These data were supported by a reduction in symptoms and symptomatic use of ventolin within the salmeterol group which was not observed in the placebo group. In contrast, no changes in differential cell counts, mediator concentrations, T-cell numbers or markers of T-cell activation were

Correspondence: S. Durham, Upper Respiratory Medicine, Imperial College School of Medicine at National Heart and Lung Institute, Dovehouse Street, London, SW3 6LY, UK.

observed in bronchoalveolar lavage fluid. Similarly, in bronchial biopsy specimens, there were no changes in inflammatory cell numbers or alterations in collagen deposition, nor was there any evidence of mast cell degranulation as determined by electron microscopy.

One explanation for the discrepancy between the apparent effects of salmeterol on inflammatory changes during allergen-induced late asthmatic responses and the lack of anti-inflammatory effects during natural asthma, may be the development of tachyphylaxis to these anti-inflammatory effects during prolonged treatment. For example, tachyphylaxis for the bronchoprotective effects of salmeterol against various inducers of asthma, but not the bronchodilating effect of salmeterol, has been observed during its long-term use [27]. The findings by ROBERTS *et al*. [26] in patients with day-to-day asthma suggest that 6 weeks of treatment with the recommended doses of inhaled salmeterol, whilst providing effective bronchodilation, has no significant anti-inflammatory effects on the bronchi. The clinical implication is that inhaled salmeterol should not be prescribed alone but rather combined with effective anti-inflammatory therapy, generally inhaled corticosteroids, and with the advice to avoid any provoking factors for asthma where possible.

References

1. Kesten S, Chalman KR, Broder I, *et al*. A three-month comparison of twice daily inhaled formoterol *versus* four times daily inhaled albuterol in the management of stable asthma. *Am Rev Respir Dis* 1991; 44: 622–625.
2. Pearlman DS, Chervinsky P, LaForce C, *et al*. A comparison of salmeterol with albuterol in the treatment of mild to moderate asthma. *N Engl J Med* 1992; 327: 1420–1425.
3. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol *versus* higher dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994; 344: 219–224.
4. Woolcock A, Lundback B, Ringdal N, Jaquesa LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996; 153: 1481–1488.
5. Pauwels RA, Lofdahl CG, Postma DS, *et al*. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *New Engl J Med* 1997; 337: 1405–1411.
6. Pizzichini MMM, Kidney JC, Wong BJO, *et al*. Effect of salmeterol compared with beclomethasone on allergen-induced asthmatic and inflammatory responses. *Eur Respir J* 1996; 9: 449–455.
7. Weersink EJM, Aalbers R, Koeter GH, Kauffman HF, De Monchy JGR, Postma DS. Partial inhibition of the early and late asthmatic response by a single dose of salmeterol. *Am J Respir Crit Care Med* 1994; 150: 1261–1267.
8. Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1996; 109: 953–956.
9. Bhagat R, Kalra S, Swystun VA, Cockcroft DW. Rapid onset of tolerance to the, bronchoprotective effect of salmeterol. *Chest* 1995; 108: 1235–1239.
10. Ramage L, Lipworth BJ, Ingram CG, Cree LA. Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994; 88: 363–368.
11. O′Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2-agonists in asthma. *N Engl J Med* 1992; 327: 1204–1208.
12. Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma: effect on bronchial responsiveness during and after treatment. *Am J Respir Crit Care Med* 1995; 152: 1170–1174.
13. Church MK, Hiroi J. Inhibition of IgE-dependent histamine release from human dispersed lung mast cells by anti-allergic drugs and salbutamol. *Br J Pharmacol* 1987; 90: 421–429.
14. Butchers PR, Vardey CJ, Johnson M. Salmeterol: a potent and long acting inhibitor of inflammatory mediator release from human lung. *Br J Pharmacol* 1991; 104: 672–676.
15. Whelan CJ, Johnson M. Inhibition by salmeterol of increased vascular permeability and granulocyte accumulation in guinea-pig lung and skin. *Br J Pharmcol* 1992; 105: 831–838.
16. Howarth PH, Durham SR, Lee TH, Kay AB, Church MK, Holgate ST. Influence of albuterol, cromolyn sodium and ipratropium bromide on the airway and circulating mediator responses to allergen provocation in asthma. *Am Rev Respir Dis* 1985; 132: 986–992.
17. Twentyman OP, Finnerty JP, Harris A, Palmer J, Holgate ST. Protection against allergen-induced asthma by salmeterol. *Lancet* 1990; 336: 1338–1342.
18. Pedersen B, Dahl R, Larsen BB, Venge P. The effect of salmeterol on the early and late phase reaction to bronchial allergen and postchallenge variation in bronchial reactivity, blood eosinophils, serum eosinophil cationic protein and serum eosinophil protein X. *Allergy* 1993; 48: 377–382.
19. Dente FL, Banclairi L, Bacci E, *et al*. Effect of a single dose of salmeterol on the increase in airway eosinophils induced by allergen challenge in asthmatic subjects. *Thorax* l999; 54: 622–624.
20. Gauvreau GM, Doctor J, Watson RM, Jordana M, O′Bryne PM. Effects of inhaled budesonide on allergen-induced responses and airway inflammation. *Am J Respir Crit Care Med* 1996; 154: 1267–1271.
21. Trigg CJ, Manolitsas ND, Wang J, *et al*. Placebo controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med* 1994; 150: 17–22.
22. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide and a β_2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992; 90: 32–42.
23. Robinson DS, Hamid Q, Ying S, *et al*. Prednisolone treatment in asthma is associated with modulation of bronchoalveolar lavage cell IL-4, IL-5 and IFN-gamma cytokine gene expression. *Am Rev Respir Dis* 1993; 148: 401–406.
24. Bentley AM, Hamid Q, Robinson DS, *et al*. Prednisolone treatment in asthma: reduction in the numbers of eosinophils, T-cells, tryptase-only positive mast cells (MCT) and modulation of interleukin-4, interleukin-5 and interferon gamma cytokine gene expression within the bronchial mucosa. *Am J Respir Crit Care Med* 1996; 152: 551–556.
25. Gardiner PV, Ward C, Booth H, Allison DJ, Hendrick, Walters EH. Effect of eight weeks treatment with salmeterol on bronchoalveolar lavage inflammatory indices in asthmatics. *Am J Respir Crit Care Med* 1994; 150: 1006–1011.
26. Roberts AJ, Bradding P, Britten KM, *et al*. The effect of the long-acting inhaled β_2-agonist salmeterol xinafoate on indices of airway inflammation in asthma. *Eur Respir J* 1999; 14: 275–282.
27. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long term effects of a long-acting β_2-adrenoceptor agonist, salmeterol on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992; 327: 1198–1203.