

A European Respiratory Review on Salmeterol

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World-wide the majority of patients with asthma are controlled with bronchodilator drugs. Such medication provides rapid symptomatic relief and may be all that is required for the treatment of mild asthma. In patients with more than occasional symptoms, however, conventional beta-agonist therapy is inadequate to provide consistent relief, particularly at night [1]. A logical progression was the development of longer acting beta-agonists and the latest issue of the European Respiratory Review reviews one of the first of this class of drug to become available - salmeterol.

The pharmacokinetic profile of the conventional beta-agonist with a therapeutic effect of 4-6 h is such that the drug becomes ineffective just as the asthmatic needs it most, at the nadir of the morning dip in lung function. The use of sustained release preparations of theophylline and beta-agonists have sought to combat this problem [2-3], but in general additional bronchodilation has been obtained at the expense of a marked increase in side effects. In Europe, and particularly the UK, poor symptom control has been taken as evidence for the need for inhaled steroids [4]. Yet, despite inhaled steroids many patients still report breakthrough symptoms. To fill this gap in the symptom control several pharmaceutical houses have sought to develop long-acting beta-agonists. The pharmacology of these agents has been extensively reviewed in this journal [5].

A thoroughly investigated long acting beta-agonists is salmeterol. Pharmacological development of this molecule, led by Dr R Brittain of Glaxo Group Research, was on the rational basis that modification of the salbutamol molecule by incorporation of a long carbon 'tail' might result in an increased duration of action. Indeed, the saligenin ethanolamine moiety of salbutamol is unmodified in salmeterol. This is the part of the molecule which binds to the ligand binding site of the beta-receptor with the long carbon tail anchored by a non-polar group at an "exocyte". Binding at this latter site causes salmeterol's prolonged duration of action by retaining the drug at the beta receptor even when the ligand binding site is blocked by a beta-blocker. Thus in the guinea pig trachea the relaxant effects of salmeterol return when the beta-blocker is washed out of the preparation [6]. It is perhaps surprising that the addition of a carbon tail to salbutamol will alter the drug's binding characteristics to

the beta-receptor, yet binding studies show that salmeterol has a 50 fold greater affinity than salbutamol [6]. *In vitro* and *in vivo* animal pharmacology confirms salmeterol as a highly potent, selective and long acting beta-agonist.

Several pre-clinical and clinical studies have now been performed in man. ULLMAN and SVEDMYR [7] were the first to demonstrate that prolonged bronchodilation could be achieved with inhaled salmeterol. Dose ranging studies have demonstrated maximum bronchodilation with 50 µg salmeterol in mild asthma and 100 µg in moderate to severe asthma [8]. This latter dose is associated with an increase in beta₂-mediated side effects and the clinician must strike a balance in the risk/benefit ratio for each individual patient. Using these doses of salmeterol in a *b.d.* regimen a highly significant increase in morning and evening peak flows have been demonstrated with associated improvement in nocturnal symptoms. In many patients the morning dip is completely abolished. Salmeterol also provides prolonged protection against a variety of challenges such as methacholine and histamine inhalation and exercise-induced bronchoconstriction. I am convinced for the evidence that has accumulated so far that salmeterol is a potent long-lasting beta₂-agonist and as such is an important addition to our armamentarium.

Two key questions remain to be answered, however. Does salmeterol have any additional useful effect apart from bronchodilation? Where should we place salmeterol in our plan of asthma management?

The most controversial claim made for salmeterol is that it has significant anti-inflammatory properties. Conventional beta-agonists have long been known to have effects on *in vitro* models of inflammation such as mast cell degranulation [9]. However, these actions have not been translated into any clinically useful anti-inflammatory properties, and conventional beta-agonists are not regarded as anti-inflammatory drugs. In *in vitro* systems salmeterol has similar actions to salbutamol, but with the expected prolonged duration of action. Whether this sustained action may lead to a decrease in inflammation, possibly by inhibition of eosinophil infiltration, is unknown. One lavage study of asthmatic subjects has reported no change in differential cell count, although there was a decrease in bronchoscopically observable inflammatory score and indirect measures of macrophage activation [10]. Whether this effect also occurs with long-term treatment with a conventional beta-agonist is unknown.

One study has addressed the effects of salmeterol on antigen challenge and the late response in atopic asthma [11]. With salmeterol pretreatment the authors observed that FEV₁ and PC₂₀ histamine remained above baseline after antigen challenge. They conclude that drug treatment abolished the late response. We have disagreed with this conclusion [12] and find clear evidence of a late response in their data, the baseline having been shifted by the prolonged bronchodilating action of salmeterol.

To demonstrate conclusively that salmeterol has genuine anti-inflammatory properties will be difficult. Biopsy studies from asthmatic volunteers may be helpful, but may be prone to sampling error. An alternative is to use other organs such as the nose or skin to investigate potential non-bronchodilating properties.

Many physicians have adopted a step-wise approach to the treatment of asthma which broadly follows the guidelines laid down by the British Thoracic Society [4]. The introduction of salmeterol may lead to a reappraisal of these guidelines particularly as it comes at a time when the whole question of the use of beta-agonists is under critical appraisal [13]. Will similar problems arise with the long acting beta-agonists? Preliminary data from Glaxo are encouraging; of 4658 patients who have received salmeterol in controlled comparative trials the incidence of severe asthma requiring hospital admission was 1.2% compared with 2% in 3466 control patients on other medication [14]. The incidence of asthma was, however, almost double in the first three months of administration compared with the rest of the year. Douglas and FITZPATRICK [15] report the case of a 48 yrs old patient with steroid-dependent asthma who died shortly after starting salmeterol 100 µg b.d.. The first patient I placed on salmeterol died 10 days after starting treatment. Until more evidence is available I believe a cautious approach to the use of salmeterol is indicated and it should be reserved for those patients having troublesome nocturnal symptoms despite maximum inhaled corticosteroid therapy.

There is no doubt that salmeterol is the first in a new class of agent, the long-acting beta-agonists. If our initial hopes are confirmed, these drugs will

represent the first genuine advance in asthma therapy for over a decade.

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