Different bronchodilating effect of salmeterol and formoterol in an adult asthmatic

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Salmeterol and formoterol have been designed to have prolonged duration of action at the β2-receptors [1]. The clinical bronchodilator efficacy of both salmeterol and formoterol appears to be similar to that of salbutamol and terbutaline, although a slower onset of action has been observed for salmeterol [2]. Both drugs induce symptomatic relief of wheezing and breathlessness, with a duration of action of up to 12 h [3]. Compared to salbutamol and terbutaline, both salmeterol and formoterol possess a longer side-chain. The salmeterol side-chain is considerably longer than that of formoterol, and it has been suggested that this long side-chain binds to an exoreceptor near the β-receptor, which may explain the prolonged duration of action [4, 5]. From a structural point of view, it seems unlikely that the long action of formoterol is due to the same mechanism [3]. So far, no direct comparative studies concerning clinical efficacy of formoterol and salmeterol have been published. However, it has been observed that the effect of formoterol may vary from individual to individual [6]; whereas, this apparently has not been observed for salmeterol.

Based on the presumed differences in mechanism of action between formoterol and salmeterol, it may be anticipated that the bronchodilating effect of the two drugs could differ in some patients with asthma. We report on a patient with long-standing asthma, who had pronounced differences in the bronchodilator effect of formoterol and salmeterol.

Case report

A 38 year old man was admitted to our clinic in 1990; he had been suffering from typical bronchial asthma since early childhood. During the two weeks prior to his first visit at the clinic, he had experienced persistent symptoms of asthma (including nocturnal symptoms) and had used inhaled salbutamol (0.2 mg 10–12 doses/day), with only modest subjective effect. Spirometry revealed a moderate obstructive ventilatory defect (baseline forced expiratory volume in one second (FEV1) 1.71 l (45% predicted); forced vital capacity (FVC) 2.90 l; height 1.73 m), with substantial improvement after administration of salbutamol (0.5 mg) and ipratropium bromide (40 μg) (FEV1, 2.35 l (61% pred); and FVC 3.01 l) (fig. 1). Skin-prick testing showed a positive reaction to house dust mite, and the number of blood eosinophils was slightly increased (0.48x10^9 l^-1); whereas the chest X-ray was normal. As the patient had been operated for peptic ulcer in 1984, it was decided not to give systemic corticosteroid. Thus, treatment with high-dose inhaled corticosteroid (beclomethasone dipropionate, 1 mg b.i.d.) was initiated. Apart from an increase in FVC, spirometry (FEV1, after administration of bronchodilator 64% pred) was unchanged 10 weeks later strongly suggesting steroid-resistant asthma. The patient had previously been treated with corticosteroids by his general practitioner on two occasions, without subjective improvement in condition (pulmonary function data not available). The
possibility of steroid-resistant asthma was also supported by lack of subjective effect, i.e. the patient continued to have daily symptoms only in sufficiently relieved by use of inhaled salbutamol several times each day and night. Treatment with beclomethasone was discontinued and a trial was performed with oral salbutamol (8 mg b.i.d.), with no subjective or objective effect. When the patient was seen again in May 1991, he had an acute exacerbation of asthma (FEV₁ 26 and 47% pred, pre and post bronchodilator respectively) and treatment with formoterol (24 μg b.i.d.) was added to the treatment with inhaled salbutamol. Six weeks later a substantial improvement in spirometry (FEV₁ 58 and 66% pred, respectively) was observed; being also greater than spirometric values obtained at the first visit. More importantly, at least to the patient, the nocturnal symptoms had vanished and he was now able to play football without having symptoms of exercise-induced bronchoconstriction. At that time, formoterol was not marketed in Denmark and, because of shortage of supplies, treatment was changed to salmeterol (100 μg b.i.d.). This led to another substantial decrease in spirometric values, especially in baseline FEV₁ (34% pred), and an increase in the need for inhaled salbutamol for relief of symptoms. When treatment was changed back to formoterol, spirometric values (and symptoms) returned to the level obtained previously. On continued treatment with formoterol, spirometric values and the clinical condition have remained stable for more than 12 months (FEV₁ >70% pred).

To verify the difference in response to formoterol and salmeterol, the patient was tested on two separate days in April 1993. He was asked not to use an inhaled bronchodilator for at least 12 h before the tests. At 8 a.m. after baseline spirometric values had been obtained, the patients was given either 24 μg formoterol or 100 μg salmeterol [3] (blind to the patient) from a metered-dose inhaler connected to a spacer device system. Measurements of FEV₁ and FVC were repeated after 15, 30 and 60 min; whereafter, spirometry was repeated 15 min after inhalation of 5 mg of salbutamol. Baseline FEV₁ was similar on the two days (Day 1 (formoterol) 1.42 l (37% pred; and Day 2 (salmeterol) 1.53 l (40% pred). Thirty minutes after administration of formoterol, the FEV₁ had increased to 3.02 l (113%) (79% pred); whereas, it was 1.60 l (5%) (42% pred) 30 min after administration of salmeterol (fig. 2). No further improvement in FEV₁ was seen after administration of salbutamol.
Discussion

During long-term treatment, this asthmatic patient had a striking difference in clinical efficacy of formoterol and salmeterol. This was later verified by testing the acute bronchodilatory effect of the two drugs in a single-blind design. As the patient was given equipotent doses of the two drugs [3], it seems unlikely that the difference in response was caused by too low a dosage of salmeterol. These observations imply that the clinical efficacy of these long-acting β₂-agonists may differ in individual patients, and that a less favourable response to, for instance, salmeterol should not preclude a trial of treatment with formoterol.

The mechanism underlying the difference in response to the two long-acting β₂-agonists observed in our patient is unknown. Compared to the short-acting β₂-agonists, both salmeterol and formoterol possess a considerably longer side-chain, which may explain the longer duration of action [4, 5]. The long-lasting effect of salmeterol is probably due to binding of the long side-chain to an exoreceptor near the β-receptor [4, 5], whereas it seems unlikely that this is also the mechanism behind the long action of formoterol [3]. The observed difference in response to the two drugs might, therefore, be caused by an inherited lack of this so-called exoreceptor, or a structural variation in it preventing stable binding of the salmeterol molecule. Another possible explanation might be an inherited variation on the β₂-receptors, likewise preventing a long-lasting effect of the drug. Future studies comparing the mechanisms behind the long-lasting effect of salmeterol and formoterol should probably explore the question of possible genetic differences in the β₂-receptors. Based on in vitro studies, it has, however, recently been suggested that the mechanism underlying the long duration of action of both formoterol and salmeterol is a physicochemical partitioning of these lipophilic drugs into the lipid bilayer of the cell membrane [7]. Once having partitioned into the bilayer, the β₂-agonists are assumed to slowly wash-out into the aqueous biophase, thereby becoming available to interact with the active site of the β₂-receptor. Compared to salmeterol, formoterol is only moderately lipophilic and differences in partitioning into the cell membrane might, therefore, lead to differences in the degree of bronchodilatation observed.

When the acute response to salmeterol was tested, no improvement in FEV₁ was noted 15 min after administration of salbutamol, although the baseline FEV₁ was reduced and a good response to salbutamol had been observed earlier (without "pretreatment" with salmeterol). However, in vitro studies using guinea-pig trachea performed by JEPPSON et al. [8] have apparently shown that salmeterol, in comparison with formoterol, is a partial β₂-receptor agonist. Based on this, they suggested that the presence of a partial agonist may increase the dose required for a full agonist (in situ salbutamol) obtained maximal bronchodilatation. Theoretically, at least this might explain the finding in our patient. The lack of improvement in FEV₁ after administration of salbutamol, when the patient was tested with formoterol, is probably due to the fact that maximal bronchodilatation had already been obtained by formoterol.

References