

Long-acting β_2 -adrenoceptor agonists: a new perspective in the treatment of asthma

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ABSTRACT: New long-acting β_2 -adrenoceptor agonists, formoterol and salmeterol, may soon appear in several European countries for treatment of asthma. This review examines currently available information and compares the basic pharmacology and describes the clinical effects of these new drugs. The long duration of bronchodilation seen in clinical studies seems to be similar, whereas in isolated tissues there might be a difference in the binding characteristics to the β_2 -adrenoceptor. Long-acting β_2 -agonists could have an inhibitory effect on inflammatory events related to asthma, but the clinical relevance of these effects is not clear at present. Long-term studies up to one year with both new drugs have not shown any unexpected side-effects, and no tachyphylaxis to β -adrenoceptor stimulation has been reported. Patients appear to strongly prefer the new drugs compared to the short-acting β_2 -agonists. The potential place for these drugs in the treatment of asthma is discussed and some pitfalls pointed out. It is likely that the long-acting β_2 -agonists will be beneficial to many asthmatic patients.

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β_2 -adrenoceptor agonists used as bronchodilators have played an important part in the treatment of asthma during the last 20 yrs. These selective drugs have the advantage over nonspecific β -adrenoceptor agonists such as isoprenaline, being devoid particularly of cardiac side-effects [1]. Selective β_2 -agonists such as salbutamol, terbutaline and fenoterol are currently the most potent and effective bronchodilators available for the treatment of asthma, particularly when administered by inhalation [1]. They induce prompt symptomatic relief of wheezing and breathlessness with a duration of action of 3-5 h. Repeated use of β_2 -adrenoceptor agonists does not appear to lead to tachyphylaxis on the bronchodilatory effect in asthmatics [1].

β_2 -adrenoceptor agonists are also potent in inhibiting mast cell degranulation [2]. However, their effect on various manifestations of the inflammatory events in asthma has been controversial [3]. Studies of airway microvascular leakage has provided conflicting results, and there is evidence to suggest that β_2 -agonists do not inhibit activation of human eosinophils and alveolar macrophages [4, 5]. It has also been difficult to show any effect of the β_2 -adrenoceptor agonists on the late phase reaction after allergen provocation [6]. Therefore, currently available β_2 -agonists may not modify the inflammatory process of asthmatic airways, and concomitant treatment with an inhaled glucocorticoid is recommended, particularly if regular use of inhaled β_2 -adrenoceptor agonist is needed to control symptoms.

A new group of β_2 -adrenoceptor agonists, formoterol and salmeterol, characterized by their prolonged bronchodilator effect, has been under development during the last few years. In clinical studies, formoterol was found to have a long duration of bronchodilation when given by inhalation but when given by oral route its duration of action was similar to that of salbutamol [7]. Salmeterol was the result of a specific research programme to design long-acting bronchodilators by molecular modification of the β_2 -adrenoceptor agonist salbutamol [8-11]. Apart from their improved duration of action, these new drugs, salmeterol and formoterol, may possess other properties of particular relevance to asthma.

Salmeterol and formoterol may become available for prescription in several European countries within the next few years. In this article we will review the basic and clinical pharmacological profiles of these new β_2 -agonists, and in the light of the information available so far we will speculate on how these drugs may be used in the treatment of asthma and pinpoint some of the possible problems that may arise with these drugs.

Basic pharmacology

The chemical structure of the two new compounds are shown together with salbutamol, terbutaline and fenoterol in figure 1 [11-13]. Both formoterol and

salmeterol possess a longer side-chain than salbutamol and terbutaline. 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_2 -receptor; the exoreceptor may help to anchor the β_2 -agonist to its receptor and this may explain the prolonged duration of salmeterol [11–14]. From a structural point of view it seems unlikely that the long action of formoterol is due to the same mechanism.

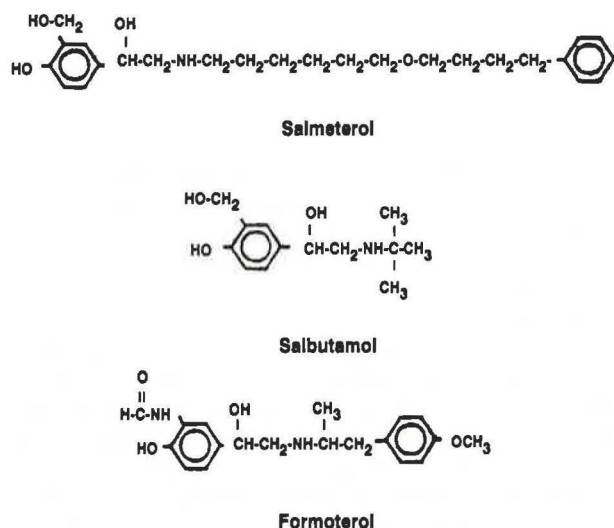


Fig. 1. - Chemical structures for salbutamol, formoterol and salmeterol.

Both compounds are highly selective for β_2 -adrenoceptors [9–13]. Formoterol is about 200 times more potent in inducing relaxation of the precontracted guinea-pig tracheal smooth muscle than in increasing the atrial rate in isolated guinea-pig atria. By comparison salbutamol was 17 times more potent on the trachea than on the atria [13]. Formoterol and salmeterol are much more potent than salbutamol in the guinea-pig trachea, as seen both with extratracheal and intratracheal administration (table 1) [15].

The time of onset for the bronchodilator effect could be important when the drugs are used in the clinical situation. *In vitro*, salmeterol has a markedly increased time to half maximal relaxation, about 17 min in a carbachol-contracted guinea-pig trachea, whereas salbutamol and formoterol exerted half maximum relaxation within 2 min [15].

Table 1. - Potency (pD_2) for some β_2 -adrenoceptor agonists, measured as inhibition of the increase in intratracheal pressure induced by vagal nerve stimulation

Compound	Extratracheal admin pD_2	Intratracheal admin pD_2
Salbutamol	7.32±0.13	5.75±0.09
Formoterol	9.23±0.11	8.51±0.25
Salmeterol	8.03±0.26	7.97±0.26

Mean±SEM. Data from [15].

Salmeterol was shown to have a long duration of effect on isolated guinea-pig trachea and human bronchial tissue, and a sustained effect for many hours has been shown [9]. Also with formoterol a prolonged bronchodilator effect has been demonstrated *in vitro* [15, 16]. In one study the remaining β -stimulating effect on isolated guinea-pig trachea after wash-out and continuous flushing of the organ baths for 1 h was for salbutamol (0.1 μ M) only 9±4%, whereas for formoterol (10 nM) it was 78±7% and for salmeterol (50 nM) it was 93±7%. Thus, *in vitro* in the guinea-pig trachea the duration of the relaxation after continuous washing was longer for salmeterol than for formoterol [16]. In other *in vitro* models and with different doses the difference between salmeterol and formoterol has been more pronounced, with a longer remaining effect for salmeterol than for formoterol [15, 17, 18]. In a study of the effects of salmeterol, formoterol and salbutamol on the binding of (125 I) iodopindolol (125 IPIN), a β_2 -antagonist, in rat lung membranes, both salmeterol and formoterol had similar affinities (53 and 76 nM, respectively), compared to 2.5 μ M for salbutamol. Preincubation of membranes with salmeterol prevented 125 IPIN binding, but both salbutamol and formoterol were rapidly displaced by 125 IPIN [18]. Similar studies need to be performed on human lung membrane preparations.

Lipophilicity may be related to the long duration of bronchorelaxation for these drugs. One study [15] showed that the octanol/water distribution coefficient, as a measurement of lipophilicity, was low for salbutamol, whereas formoterol was lipophilic, and salmeterol was highly lipophilic. Other β_2 -adrenoceptor agonists were also tested, and a relatively good correlation between the lipophilicity and the *in vitro* duration of action was seen. However, the lipophilicity may not be the only explanation, as some β_2 -agonist drugs have a high lipophilicity without having a prolonged duration of action.

The prolonged duration of effect *in vivo* is unlikely to be due to effects on the airway epithelium, as there was no difference in duration of relaxant effect in guinea-pig tracheal rings with or without epithelium [16].

The effect of salmeterol can be blocked by sotalol, a β_2 -antagonist but reasserts itself after wash-out [11]. In a recent comparison of salmeterol and formoterol in carbachol-contracted guinea-pig tracheal rings, treated with supramaximal salmeterol (1 μ M) and formoterol (50 nM) doses, sotalol (10 μ M) rapidly reversed the relaxation in all rings. After wash-out procedures and 30 min continuous flushing of the muscle baths the effect of salmeterol and formoterol reasserted itself to a similar level as after the first treatment. In rings treated with supramaximal salbutamol doses there was no reassertion of the relaxation after sotalol treatment followed by wash out and flushing. After a second sotalol treatment the wash-out procedures and washing was repeated with a reassertion of the relaxant effect similar to that seen after the first washing period for formoterol and salmeterol, respectively [16]. These studies suggest that both compounds are bound in the smooth muscle membrane adjacent to the β -receptor, and both compounds

can reactivate the receptor after β -blockade and wash-out in the baths. There may be quantitative differences between the two compounds, and it is impossible to say whether the binding in the membrane is of a similar kind. It is possible that salmeterol has its long duration due to the long side-chain which possibly binds to the "exoreceptor", whereas formoterol with a high receptor affinity combined with high lipophilicity is readily rebound to the receptor after β -blockade.

Anti-inflammatory effects

Asthma is now considered as a chronic inflammatory disease of the airways and it is therefore of interest to know whether these newer, more potent, β_2 -agonists possess anti-inflammatory properties.

The effect of the new drugs on the release of inflammatory mediators has been partly evaluated. Formoterol was shown to be 400 times more potent than salbutamol in inhibiting the release of histamine from sensitized human lung *in vivo* [2]. Similar results have been achieved in studies of histamine release from human basophils and human lung mast cells [19]. Formoterol was also effective in inhibiting allergen-induced release of leukotrienes in sensitized rats lungs and human lungs, and in that respect it is about 40 times more potent than salbutamol [20]. Formoterol was more potent than salbutamol in inhibiting the release of hydrogen peroxide and intracellular calcium mobilization from guinea-pig eosinophils stimulated by leukotriene B_4 [21]. Salmeterol was also 5–20 times more active than salbutamol in preventing the release of histamine, leukotriene C_4 and D_4 and prostaglandin D_2 from sensitized human lung fragments, and has a considerably longer duration of effect than salbutamol [8]. In human alveolar macrophages salmeterol inhibited the release of thromboxane B_2 after zymosan stimulation, but this effect was unaffected by propranolol, indicating that salmeterol may inhibit cellular activation independently of β_2 -adrenoceptors [22]. By contrast the inhibitory effect of formoterol was prevented by β -adrenoceptor blockade [21]. These early results may indicate differing anti-inflammatory mechanisms for these β_2 -agonists.

Studies of allergic responses in the skin may indicate potential anti-inflammatory effects of the new β_2 -agonists. Inhibition of early- and late-phase reactions after cutaneous injection of anti-IgE by formoterol or

terbutaline was evaluated in healthy volunteers [23, 24]. Both formoterol and terbutaline had an initial inhibitory effect on the flare and wheal reaction with a considerably greater duration of effect for formoterol (>24 h) than for terbutaline (8 h) [23]. The oedematous late phase reaction was also more intensively inhibited by formoterol than by terbutaline at doses which had the same inhibitory effect on acute flare and wheal reactions [24]. The prolonged stimulation achieved by a long-acting, β_2 -adrenoceptor agonist may be more effective in inhibiting inflammatory events in the tissue.

In sensitized dogs both salbutamol and formoterol showed a protective effect on acute airway response to ragweed antigen challenge. However, only formoterol protected against airway hyperresponsiveness to acetylcholine observed at 5 h after allergen provocation. Formoterol also blunted the eosinophil influx measured in bronchoalveolar lavage whereas salbutamol was ineffective. Salbutamol and formoterol both blocked histamine release, but neither influenced leukotriene production [25].

In a study of the late-phase response in allergic asthmatic patients [26], salbutamol had a small protective effect on the late-phase response, but formoterol had a more pronounced effect. This also indicates that a long-acting β_2 -adrenoceptor agonist is more effective on the inflammatory events following allergic provocation. Salmeterol inhibits the early and late-phase responses, and the increase in bronchial responsiveness after challenge in asthmatic subjects (Twentyman *et al.*, *Lancet*, 1990, 336, 1338–1342). Formoterol was also much more potent than salbutamol in inhibiting airway microvascular leakage induced by histamine in the guinea-pig [27].

Overall, these data suggest that the new long-acting β_2 -agonists may possess inhibitory effects against several aspects of the inflammatory process in asthma. The clinical relevance of these effects is not clear at present.

Clinical studies

Potency

In clinical studies both formoterol and salmeterol are more potent as β -stimulating drugs than the short-acting β_2 -agonists salbutamol, terbutaline and fenoterol. Table 2 shows equipotent doses of the drugs and as

Table 2. – Clinical characteristics for some β_2 -adrenoceptor agonists

	Equipotent doses for inhalation	Duration of bronchodilation	Duration of protective effect	Onset of action
	μg	h	h	
Formoterol	6–12	12	12	rapid
Salmeterol	25–50	12	12	not determined
Salbutamol	100	3–5	2–3	rapid
Terbutaline	250	3–6	2–3	rapid
Fenoterol	100	3–6	2–3	rapid

comparison we have chosen 100 μg salbutamol, 250 μg terbutaline and 100 μg fenoterol as equipotent doses when given by the inhaled route [28–30]. The corresponding dose for formoterol is 6–12 μg and for salmeterol 25–50 μg [7, 31–34].

Selectivity

Selectivity for the β_2 -adrenoceptor has in clinical studies been shown to be similar for the new drugs and the old drugs. Formoterol was studied in cumulative dose-response experiments with both oral and inhaled administration. Similar increases in heart rate were observed for the same degree of bronchodilation when comparing salbutamol and formoterol [7]. For salmeterol no cumulative experiments have been performed, but single dose clinical studies have indicated that salmeterol has the same β_2 -selectivity as salbutamol [35].

Onset of action

The increase in specific airway conductance at one min after inhalation of formoterol (12, 24 and 48 μg) is more pronounced than after 0.2 mg salbutamol [36, 37]. Similar results were achieved in other comparisons with terbutaline and salbutamol [38, 39]. Thus, there is no evidence for a delayed onset of effect with formoterol. Studies with salmeterol have shown a tendency towards a slower onset of action [31], but evaluation of the effect during the first minutes after inhalation has not been performed. No direct comparison between salmeterol and formoterol has been performed on the question of onset of action.

Duration of bronchodilation

Formoterol and salmeterol have a bronchodilating effect lasting up to 12 h, as has been shown in several studies. Formoterol was studied in an 8 h study, in 8 asthmatic patients, and inhaled formoterol (6 μg) and inhaled salbutamol (0.1 mg) induced a rapid bronchodilation, up to about 80% of maximum achievable response. With salbutamol the bronchodilator effect had disappeared after 4–5 h, whereas 8 h after formoterol about 75% of the initial response remained [7, 40]. In several other later studies on formoterol a 12 h duration of effect has been shown both in adults [34, 36, 41, 42] and in children [32, 33, 43]. A prolonged bronchodilator effect has also been shown in healthy smokers and nonsmokers [44]. It should be noted that the duration of effect may vary from individual to individual, and some asthma patients seem to lose the effect after 9–10 h [41, 45]. However, in one study the median duration to return to baseline forced expiratory volume in one second (FEV_1) was greater than 12 h for 12 and 24 μg formoterol [41].

Salmeterol was studied in a similar study in 8 asthmatic patients, and a good sustained bronchodilation was achieved for more than 12 h [31, 35]. Other studies have confirmed the 12 h duration for salmeterol [46–49]. An individual variation of duration of bronchodilation has not been commented upon in these presentations. There are no direct comparative studies between formoterol and salmeterol concerning clinical bronchodilating effect.

Duration of protective effect against bronchoconstrictor challenges

Acute studies of the protective effect on provoked bronchoconstriction in asthma patients or in normal individuals have been performed for both drugs. A prolonged duration of the protective effect up to 12 h against methacholine in asthmatic patients has been demonstrated [50, 51]; one study showed protection lasting for at least 5 h [52]. In children the provocative methacholine dose remained elevated for more than 12 h after formoterol treatment [53, 54]. Protection against histamine in children showed similar duration after formoterol treatment [54]. For salmeterol the protection against histamine-induced bronchoconstriction in healthy subjects had a duration up to 12 h, whereas salbutamol only showed a protective effect after 1 h but not after 4 h [55]. In asthmatics salmeterol also had a protective effect up to 12 h for methacholine-induced bronchoconstriction [56].

Exercise-induced bronchoconstriction has been evaluated in some studies with formoterol. Both in adults and in children it had a protective effect which lasted for at least 8 h [54, 57–59].

One study with formoterol (20 μg) showed a protection against the late-phase allergic reaction, an effect more pronounced than the protection achieved by salbutamol (500 μg) [26]. Both drugs had an effect on the early allergic response.

Long-term effect in asthma

Formoterol treatment for up to two weeks was studied in a cross-over study in 20 asthmatic patients [60]. Peak expiratory flow values, maximum as well as minimum values, during the days were significantly better during the formoterol treatment (12 μg *b.i.d.*, and extra doses as and when needed) compared to salbutamol (0.2 mg *b.i.d.* plus extra doses). The need for additional doses of bronchodilator decreased significantly. Subjective evaluation of symptoms was better both during day and night during formoterol treatment compared to the values during salbutamol treatment. The evaluation of tachyphylaxis to, β -stimulation was performed with dose-response curves for increasing doses of salbutamol up to 1.3 mg. Before and after 2 wks of salbutamol treatment the dose-response curves were almost identical, similar to the pre-formoterol curve. After the formoterol

treatment period, mean basal FEV₁ level was higher and FEV₁ increased further after the highest dose of salbutamol. Thus, there was no evidence of tachyphylaxis during this two week treatment period [60]. There was a marked preference for formoterol; 15 preferred the formoterol period, two preferred the salbutamol period and three could not make a choice [60].

Another one month study with formoterol and salbutamol has recently been published with very similar results [61]. In a 3 month study of 301 patients in parallel groups comparing 12 µg formoterol *b.i.d.* to salbutamol 200 µg *q.i.d.*, formoterol treatment gave higher morning peak flow values, fewer acute asthma attacks, with less rescue medication [62]. In a smaller parallel group study (66 patients) no difference was shown for formoterol compared to terbutaline, but there was a trend for decreased use of rescue medication in the formoterol-treated group [63].

A two week cross-over study has been performed with salmeterol (50 µg *b.i.d.*) compared to salbutamol (200 µg *q.i.d.*) in 12 patients [64]. Ten patients preferred salmeterol and two could not make a choice. Peak flow measurements improved and the use of rescue medication decreased during the salmeterol treatment. In addition, there was no evidence of tachyphylaxis. Subjective evaluation of sleep quality and breathlessness was better after salmeterol treatment. In a multicentre study, 692 patients were randomized to 3 different dose levels of salmeterol. It showed that there was a dose-dependent improvement of peak flow, fewer episodes of nocturnal awakenings, a lower requirement of additional bronchodilator usage and no evidence of tachyphylaxis [65].

Other studies have evaluated the effect of the new β₂-agonists on nocturnal asthma. Both formoterol and salmeterol had a protective effect on nocturnal wheeze [66–69], and this effect was maintained for 1 yr in one study with formoterol [67]. One study could not show any difference between formoterol and salbutamol concerning nocturnal symptoms [70].

Several studies with formoterol have followed patients for up to 1 yr. Eighteen patients participated in a comparison of salbutamol 0.2 mg twice daily with formoterol 12 µg twice daily [71]. Extra doses were allowed. Ten patients were randomly allocated to treatment with formoterol and 8 with salbutamol. After 1, 2 and 3 months the patients were allowed to shift over to the other treatment if they were not satisfied with their asthma control. Two patients did not complete the study. After one year 13 of 16 patients were on formoterol showing a significant long-lasting preference for this drug. Dose-response curves for inhaled salbutamol were recorded repeatedly during the study. No evidence of development of tachyphylaxis was found. Peak flow values were maintained at a high level, similar to the level these patients reached during the initial formoterol treatment. Other studies have also found a sustained good effect of formoterol up to 1 yr without any sign of tachyphylaxis to the β-stimulating effect [67, 72, 73].

To date only two studies in children have evaluated bronchial hyperresponsiveness during prolonged treatment with formoterol [53, 54]. These studies have not shown any enhanced responsiveness after treatment for 3 [54] or 12 months [53]. It has been argued that short-acting β₂-agonists such as terbutaline transiently increase bronchial hyperreactivity on discontinuing treatment [74], but this has not been demonstrated with formoterol in the two studies in children [53, 54].

More long-term studies of these new β₂-agonists on bronchial hyperresponsiveness and evaluation of effects after discontinuing treatment are warranted. Studies to examine directly inflammatory indices of the asthmatic airway such as bronchial biopsies and bronchoalveolar lavage are also needed.

Place of long-acting β₂-agonists in the treatment of asthma

Several issues need to be sorted out before the exact place of the long-acting β₂-agonists in the treatment of asthma can be determined. Although there does not seem to be any evidence for development of tachyphylaxis to the bronchodilating effect of long-acting β₂-agonists, as compared to the short-acting drugs [60, 61, 64] it is not known whether this can occur in the face of worsening or more severe asthma.

Should long-acting β₂-agonists replace short-acting β₂-agonists?

The most obvious place for the new β₂-adrenoceptor agonists may be to replace currently available short-acting β₂-agonists. Several clinical cross-over studies in stable asthmatic patients with regular use of short-acting β₂-agonists have shown a very strong preference for the new long-acting drugs compared to salbutamol [60, 61, 64]. Patients with nocturnal asthma have also shown preference for the long-acting drugs [66–69]. Thus, it seems clear that patients needing regular daily intake of short-acting β₂-agonists with or without nocturnal symptoms should be treated with the new long-acting drugs.

The duration of action may vary from patient to patient. Patients with more severe asthma have not been studied and could possibly show shorter duration of effect. Furthermore, long-acting β₂-agonists will be prescribed on a twice daily schedule and therefore the question of symptomatic relief for breakthrough symptoms is important. At the present stage it is recommended to educate the patient to seek medical help when this happens, in order to obtain specific anti-inflammatory therapy with corticosteroids. It is not clear how frequently long-acting β₂-agonists can be safely used in the face of worsening asthma. Whether a conventional β₂-agonist for rescue medication would be more appropriate is not known although, with such an approach patients need to be taught to use both short- and long-acting β₂-agonists.

If long-acting β_2 -agonists are used only for patients who are in need of the short-acting β_2 -agonists more than twice daily and who experience nocturnal symptoms, then short-acting β_2 -agonists would still be recommended for those who have symptoms on a less than daily basis. However, it seems probable that when these long-acting drugs become available, many patients will show a preference for them, as already demonstrated in several studies [60, 61, 64].

Several studies have shown that the need for rescue medication decreases with the use of the long-acting β_2 -agonists. However, the patients must be informed that they should always have the possibility to take rescue medication, in case of acute bronchoconstriction. It would then be an advantage if it is possible to be able to use the long-acting bronchodilator also as a rescue medication. Otherwise there is a risk that the patients will forget the rescue inhaler for the very few occasions when they need it.

Should separate short-acting β_2 -agonists be used as rescue medication in patients on twice-daily long-acting β_2 -agonists? Some issues must be clarified. Firstly, is the onset of action for the new drugs similar to that of short-acting β_2 -agonists? This has to be further studied in acute asthma, at least for salmeterol. Recent studies with formoterol indicate a similar onset of action for salbutamol, and therefore formoterol may relieve symptoms rapidly. Secondly, is the therapeutic range the same for the new drugs as for the old drugs? The side-effects for β_2 -adrenoceptor mediated effects are skeletal muscle tremor and palpitations, which have been shown for salmeterol and formoterol for doses exceeding recommended therapeutic doses. It seems unlikely that an acute high dose could have any serious side effect, as compared to the short-acting drugs which can be given in very high doses acutely.

Should long-acting β_2 -agonists be combined with inhaled corticosteroids?

The possible need for combining anti-inflammatory treatment when treating with a long-acting β_2 -agonist is an important issue. Symptomatic relief from a very potent bronchodilator could "mask" the underlying inflammation, thereby decreasing the compliance both from the doctor and the patient to anti-inflammatory therapy. However, the long-acting β_2 -agonist might have some useful anti-inflammatory effect. Further studies are needed to evaluate the effect of these drugs on bronchial hyperresponsiveness in a long-term perspective, and also on bronchial histology and inflammatory markers in bronchoalveolar lavage fluid.

There is presently no evidence that the long-acting, β_2 -agonists have any corticosteroid sparing effect, and inhaled corticosteroid should be introduced in patients who would regularly use either short-acting or long-acting, β_2 -agonists.

This raises the question as to whether long-acting β_2 -agonists should be given in fixed combinations with corticosteroids. This could improve patient compliance,

because both drugs are usually administered twice daily. However, the choice of doses will be limited particularly in many asthma patients who need higher doses of inhaled corticosteroids. Fixed combinations also make it difficult to use the same inhalation device for both maintenance and rescue use.

Should long-acting β_2 -agonists be used in treating acute severe asthma?

This area has not been fully evaluated. High doses of the long-acting β_2 -agonists could perhaps give a better prolonged stabilization of the acutely ill severe asthmatic. However, more information on the onset of bronchodilator action of salmeterol is needed in acute severe asthma. Studies of the effects of these new β_2 -agonists on serum potassium and oxygen saturation are also necessary in this situation particularly if these drugs are to be administered in high doses *via* nebulizers.

Conclusions

There is little doubt that the introduction of long-acting β_2 -agonists will represent a significant milestone in asthma treatment, and time will tell how this will modify our practice. More information is necessary, particularly with regard to any beneficial anti-inflammatory effect and to their use in more severe asthma. It is interesting that the two long-acting β_2 -agonists, salmeterol and formoterol, which may become available in several European countries quite soon, may have different mechanisms of action underlying their prolonged duration of bronchodilator effect. Salmeterol may be a unique drug with a long side-chain that anchors the β_2 -agonist molecule to the receptor, while formoterol appears to be an extremely potent classical β_2 -agonist. These β_2 -agonists may also differ in their activities in modulating the activation of inflammatory cells of relevance to asthma.

In clinical studies long-acting β_2 -agonists are strongly preferred by the patients when compared to the short-acting drugs. They may be particularly useful in controlling symptoms of nocturnal asthma and will most likely replace the use of slow-release theophylline or oral β_2 -agonists. If these drugs possess clinically beneficial anti-inflammatory effects, their importance in asthma treatment could be considerably more important than that of the short-acting β_2 -agonists used today. Given the information we have at present, both salmeterol and formoterol will improve the quality of life of many asthmatic patients.

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Les agonistes de β_2 -adrénorécepteurs à action prolongée: nouvelle perspective dans le traitement de l'asthme. C.G. Löfdahl, K.F. Chung.

RÉSUMÉ: De nouveaux agonistes β_2 -adrénorécepteurs à action prolongée, la formotérol et le salmétérol, vont apparaître bientôt dans plusieurs pays européens pour le traitement de l'asthme. Cette revue examine les informations actuellement disponibles. Elle compare la pharmacologie de base et décrit les effets cliniques de ces nouvelles médications. La longue durée de bronchodilatation observée dans les études cliniques semble similaire alors que dans les tissus isolés, il pourrait y avoir une différence dans les caractéristiques de liaison aux β -adrénorécepteurs. Les β_2 -agonistes à action prolongée

pourraient avoir un effet inhibiteur sur les facteurs inflammatoires de l'asthme, mais la signification clinique de ces effets n'est pas encore claire à ce jour. Des études au long cours jusqu'à un an n'ont montré aucun effet collatéral inattendu avec ces nouvelles drogues et l'on n'a rapporté aucune tachyphylaxie à la stimulation des β -adrénorécepteurs. Les patients semblent préférer nettement les nouveaux produits par comparaison aux β_2 -agonistes à brève durée d'action. On discute le rôle potentiel de ces médicaments dans le traitement de l'asthme et l'on insiste sur certains pièges potentiels. Il est vraisemblable que les β_2 -agonistes à longue durée d'action seront bénéfiques à un grand nombre de malades asthmatiques. *Eur Respir J*, 1991, 4, 218-226.