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A Benefit-Risk Assessment of Inhaled Long-Acting β_2-Agonists in the Management of Obstructive Pulmonary Disease

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Contents

Abstract

The two inhaled long-acting β_2-adrenoceptor agonists, salmeterol and formoterol, have been studied extensively since their introduction in the early 1990s. In this review we consider the evidence for their efficacy and safety in adults with asthma and chronic obstructive pulmonary disease (COPD), by reviewing long-term prospective studies in which these drugs have been compared with placebo or an alternative bronchodilator. We have also assessed safety, including data from postmarketing surveillance studies and case-control studies using large databases.

In patients with asthma, salmeterol and formoterol increase lung function, reduce asthmatic symptoms and improve quality of life when compared with placebo. Both drugs protect against exercise-induced asthma, although some tolerance develops with regular use. Tolerance to the bronchodilator effects of formoterol has also been seen, although this is small and most of the beneficial effects are maintained long-term. Both drugs have been shown to reduce asthma exacerbations but only in studies in which most patients were taking an inhaled corticosteroid. Adding a long-acting β_2-agonist provided better control than increasing the dose of inhaled corticosteroid in several studies. Long-acting β_2-agonists also provide better asthma control than use of regular short-acting β_2-agonists and theophylline. Their relative efficacy compared with leukotriene antagonists is uncertain as yet. Formoterol appears to be at least as safe and effective as a short-acting β_2-agonist when used on an 'as required' basis.

In patients with COPD, both salmeterol and formoterol offer improved lung function and reduced COPD symptoms compared with placebo, and quality of life has been improved in some studies. Some tolerance to the bronchodilating effect of salmeterol was seen in one study. Most studies have not found a significant reduction in exacerbations in COPD. Both drugs have provided greater benefit than ipratropium bromide or theophylline; there are limited data on tiotropium bromide.

The long-acting β_2-agonists cause predictable adverse effects including headache, tremor, palpitations, muscle cramps and a fall in serum potassium concentration. Salmeterol can also cause paradoxical bronchospasm. There is some evidence that serious adverse events including dysrhythmias and life-threatening asthma episodes can occur; however, the incidence of such events is very low but may be increased in patients not taking an inhaled corticosteroid.

Salmeterol 50μg twice daily and formoterol 12μg twice daily are effective and safe in treating patients with asthma and COPD. Higher doses cause more adverse effects, although serious adverse events are rare.

Long-acting β2-adrenoceptor agonists, administered by inhalation, came on to the market in the early 1990s. They were seen as a logical development from the short-acting β2-agonists, such as salbutamol (albuterol) and terbutaline, which had been used to treat episodic asthma, relieve asthmatic symptoms and prevent exercise-induced asthma since the 1960s. Bronchodilatation from the short-acting β2-agonists only lasts for 3–6 hours, however, so the drugs are not effective throughout the night. A programme to develop a β2-agonist with a longer duration of action led to the development of salmeterol,[1] whereas the discovery that formoterol had a long duration of action appears to have been more serendipitous.[2] Both salmeterol and formoterol cause prolonged bronchodilation, lasting for more than 12 hours following inhalation.[3]

The potential benefits of a long-acting β2-agonist were clear in the early 1990s[1-3] but there were also some concerns that regular treatment with a long-acting β2-agonist might lead to tolerance. These fears were fuelled by the publication of a paper by Sears et al.[4] on fenoterol in 1991, which coincided with the launch of salmeterol. The 6-month crossover study showed that asthma control was worse when subjects took the short-acting β2-agonist fenoterol on a regular basis, four times a day, compared with when they took placebo regularly and fenoterol as required. Previous smaller studies had shown that the protection afforded by β2-agonists against bronchoconstrictor stimuli was reduced when the drugs were taken regularly[5-7] and some studies had noted a rebound increase in bronchial responsiveness when β2-agonist treatment was stopped.[6-10] Both effects were attributed to tolerance, a phenomenon that is relatively easy to demonstrate with β2-agonists *in vitro*.[11] Thus, the introduction of the long-acting β2-agonists was associated with concern that tolerance would occur and the drugs might be less effective if taken on a regular basis. There were also concerns that a bronchodilator without anti-inflammatory activity would mask deteriorating asthma so that exacerbations, when they occurred, would be more severe. For these reasons both formoterol and salmeterol were subjected to large-scale studies to determine their effectiveness and adverse effects over long periods of time, something which had not occurred when the short-acting β2-agonists were introduced into clinical practice in the 1960s and 1970s.

This review is concerned with the benefit-risk assessment of long-acting β2-agonists in patients with airflow obstruction. It relies predominantly on published data from prospective randomised clinical studies in adults with asthma and chronic obstructive pulmonary disease (COPD), but it also reviews the relevant postmarketing surveillance studies and studies that have related prescription of long-acting β2-agonists with outcomes such as hospital admissions and deaths. Studies published in English were identified by searching an electronic database (Medline from 1966 to October 2003) with the terms 'salmeterol', 'formoterol' and 'long-acting beta agonist'. The references in the publications identified were also searched for previous relevant studies. In the papers that we have included in our review the dose of the long-acting β2-agonists is sometimes presented as the dose actuated in the inhaler (e.g. salmeterol 50μg or formoterol 12μg) and sometimes as the delivered dose (e.g. salmeterol 42μg or formoterol 9μg). We have given the dose the authors chose to use in the tables but for consistency in the text have converted all doses to the dose in the inhaler.

Before looking at the clinical studies, however, we briefly review the pertinent aspects of the pharmacology of formoterol and salmeterol and their effect on inflammation, as well as any pharmacological differences between the two drugs that may be relevant to the interpretation of the clinical studies.

1. Pharmacology of Formoterol and Salmeterol

1.1 Overview

The pharmacological effects of formoterol and salmeterol are due to β-adrenoceptor stimulation and these have been reviewed elsewhere.[11] The main effects on the airways are thought to be due to smooth muscle relaxation and inhibition of mediator release from inflammatory cells in the airway, such as mast cells. The drugs may also affect vascular permeability and cholinergic constrictor tone. Several studies have looked at the effect of the long-acting β_2-agonists on airway inflammation in patients with asthma, as detailed in table I.[12-21] Regular use of formoterol and salmeterol appears to have little or no effect on the inflammatory response in the airways when measured by markers of airway inflammation in sputum, bronchial biopsy or bronchoalveolar lavage, irrespective of whether patients were[12,13] or were not[14-21] taking an inhaled corticosteroid. Some studies have shown a significant change in certain cell populations. For example, salmeterol was associated with a reduction in eosinophil count in the lamina propria in one study,[13] a reduction in the number of neutrophils in another,[16] and in a third study the lymphocyte response to antigen was increased after 1 week's treatment with salmeterol compared with placebo.[21] Most of the studies have been relatively small, however, and since none of the positive findings has been reproduced consistently their significance remains uncertain.

Stimulation of β-adrenergic receptors in other organs is responsible for the systemic effects that can occur with β_2-agonists, particularly when the drugs are given in high doses or by the oral or systemic route.[11] These include tachycardia, peripheral vasodilatation, tremor and certain metabolic effects of which hypokalaemia is the most important. These pharmacological effects may predispose to dysrhythmia in vulnerable patients.

Table I. Placebo-controlled trials looking at the effects of long-acting β_2-adrenoceptor agonists on airway inflammation

Study	No. of subjects (no. receiving long-acting β_2-agonist)	Duration (wk)	Drug and twice-daily dose (μg)	% on ICS	Outcome measures							
					Eo in sputum	Eo in BAL	ECP	Eo in Br Bx	MC in BAL	MC in Br Bx	TI in Br Bx/BAL	Neu in BAL	Neu in Br Bx
Dahl et al.[17]	12 (12)	4 XO	S 50	0	-	0	↓	-	0	-	0	-	-
Gardiner et al.[12]	9 (9)	8 XO	S 50	100	-	0	-	-	0	-	-	0	-
Kraft et al.[15]	10 (10)	6 XO	S 50	0	0	0	0	-	-	-	-	0	-
Turner et al.[18]	34 (12)	3	S 50	0	0	-	0	-	-	-	-	-	-
Wallin et al.[14]a	64 (21)	8	F 24	0	-	-	-	0	-	0	0	-	-
Roberts et al.[20]	26 (14)	6	S 50	0	-	0	0	0	0	0	0	0	0
Li et al.[13]a	45 (13)	12	S 50	100	-	0	-	↓	0	0	0	-	-
Boulet et al.[21]b	16 (16)	1 XO	S 50	0	-	0	-	0	0	0	↑	0	-
Jeffery et al.[16]a	20 (20)	6 XO	S 50	0	0	0	-	0	-	-	0	0	↓
Bacci et al.[19]	30 (15)	4	S 50	0	-	0	-	-	-	-	-	-	-

a Trials with a third limb with patients taking an inhaled corticosteroid.

b In response to antigen challenge.

0 = no effect; **BAL** = bronchoalveolar lavage; **Br Bx** = bronchial biopsy; **ECP** = eosinophilic cationic protein; **Eo** = eosinophil; **F** = formoterol; **ICS** = inhaled corticosteroid; **MC** = mast cell; **Neu** = neutrophil; **S** = salmeterol; **TI** = T lymphocyte; **wk** = weeks; **XO** = crossover study design; **-** indicates not mentioned; ↑ indicates increase; ↓ indicates decrease.

1.2 Differences Between Formoterol and Salmeterol

Salmeterol and formoterol have many features in common but there are some differences in their pharmacology, which we review briefly.

1.2.1 Mechanism Underlying Their Long Duration of Action

The mechanism underlying the long duration of action of salmeterol and formoterol appears to differ. Both drugs are lipophilic and hence taken up into the lipid cell membrane. Formoterol is thought to diffuse slowly from the cell wall to the β-adrenoceptor thus stimulating the receptor over a prolonged period.[2] Salmeterol is more lipophilic than formoterol and it also has a long aliphatic side chain. Site directed mutagenesis studies suggest that the side chain anchors to an exosite on the fourth transmembrane domain of the β-adrenoceptor[22] allowing the saligenin head of the molecule to engage repeatedly with the active receptor site, and thus prolonging the drug's duration of action.

1.2.2 Speed of Onset of Action

Following inhalation, formoterol has a rapid onset of action similar to that of salbutamol,[3] whereas the onset of action with salmeterol is slower.[3] Around 70% of maximum bronchodilatation is seen within 5 minutes of inhalation of formoterol compared with nearly an hour with salmeterol.[3] Anderson[2] has suggested that the difference in onset of action relates to differences in lipophilicity. Salmeterol, being the more lipophilic, enters the cell membrane rapidly and is retained in the outer phospholipid layer from where it diffuses laterally but relatively slowly to react with the β_2-adrenergic receptor. Being less lipophilic some formoterol enters the plasmalemma where it is retained but some remains in the aqueous phase where it is able to react rapidly with β_2-adrenoceptors. The rapid onset of action of formoterol means that it can be used to relieve acute bronchoconstriction in patients with asthma (see section 2.3).

1.2.3 Efficacy

The fact that salmeterol is a partial agonist *in vitro* compared with isoprenaline (isoproterenol), whereas formoterol is a much fuller agonist,[2] is potentially important for two reasons. First, a partial agonist could produce a smaller effect (e.g. less bronchodilatation) than a full agonist, assuming there were no spare receptors and that bronchodilatation was limited by β_2-adrenoceptor activity. Second, in theory treatment with a partial agonist (e.g. salmeterol), could reduce the effectiveness of a fuller agonist (e.g. salbutamol) during an acute exacerbation of asthma by reducing receptor availability for the full agonist. In keeping with this, laboratory studies suggest that the response at which the dose-response curve plateaus is lower for salmeterol than formoterol for both protection against methacholine challenge and systemic effects.[23] There is, however, no evidence that formoterol is more effective than salmeterol in clinical practice. Nor is there good evidence to suggest that patients taking salmeterol have exacerbations that are less responsive to short-acting β_2-agonists.[24-26] One study looking specifically at this point documented the response to salbutamol in patients admitted to an emergency department with acute asthma, comparing 57 who had been taking salmeterol with 57 who had not taken a long-acting β_2-agonist prior to admission.[26] There was no difference in the increase in peak flow with salbutamol between the two groups, nor any difference in any other clinical outcome.

1.2.4 Pharmacokinetics

Formoterol and salmeterol are well absorbed from the lung and gut. Following oral administration, formoterol is largely metabolised to a glucuronide conjugate, which is mainly excreted in urine. Salmeterol is hydroxylated in the liver and eliminated predominantly in faeces.[27] When given by metered-dose inhaler some two-thirds of the systemic effects of salmeterol are due to drug absorption from the lung.[28]

1.2.5 Development of Tolerance

Long-acting β_2-agonists reduce the bronchoconstrictor response to a range of stimuli, including allergen, exercise, histamine and indirectly-acting agents such as adenosine monophosphate. However, the protective effect against such stimuli is reduced with regular use.[29-33] For example, a single dose of salmeterol reduced the bronchoconstrictor response to exercise by 66% in one study, whereas after regular use the protective effect was only 28%.[32] This loss of protection occurs with both formoterol

and salmeterol, as with the short-acting β_2-agonists. A rebound increase in bronchial responsiveness has not been seen, however, following cessation of treatment with either long-acting β_2-agonist.[29,31]

Tolerance may also be seen in terms of a reduced bronchodilator response and in this respect formoterol has been shown to cause tolerance in patients with asthma, whereas salmeterol has not (see section 2.1).

1.2.6 Systemic Effects

Following inhalation of increasing dosages, both salmeterol and formoterol have systemic effects that include an increase in heart rate and corrected QT (QTc) interval and a fall in plasma potassium and diastolic blood pressure. In single-dose studies in the laboratory, the effects are broadly similar for salmeterol and formoterol after allowing for the 4-fold difference in potency between the two drugs.[34,35]

2. Efficacy of Long-Acting β_2-Agonists in Patients with Asthma

The effects of the two long-acting β_2-agonists have been compared with placebo and/or a short-acting β_2-agonist in a large number of prospective studies in patients with asthma. Table II and table III list those of 4 weeks' duration or more. The studies have lasted for up to 80 weeks and the number of patients studied has ranged from 16 to 25 180. Most patients studied were taking a regular inhaled corticosteroid, although the proportion taking an inhaled corticosteroid in each study has varied widely between 0% and 100%.[36-78]

2.1 Comparison with Placebo

2.1.1 Lung Function

When compared with placebo, salmeterol and formoterol cause bronchodilatation which is still evident 12 hours after administration.[38,63] The increase in morning and evening peak flow was in the range of 20–40 L/min and the increase in forced expiratory volume in 1 second (FEV_1) was in the range of 100–200mL. The increase in lung function was seen in studies in which patients were taking an inhaled corticosteroid[38,41,63] and those in which they were not.[30,46] The response to salmeterol was similar in the two groups.[37,56,57]

A few studies have addressed the question of whether tolerance develops with respect to the bronchodilator effect of long-acting β_2-agonists following their long-term use. Most studies of salmeterol have found no evidence of bronchodilator tolerance in patients with asthma. These include two placebo-controlled studies that were designed specifically to address this issue.[56,57] In these studies the authors looked at the area under the curve (AUC) for FEV_1 after the morning dose of salmeterol and found no difference in the AUC between an early morning dose of salmeterol taken on day 1 and the last dose taken, at the same time of day, 12 weeks later.

Tolerance to the bronchodilator effects of formoterol has been reported in several studies. In two small studies designed to address this concern the bronchodilator response to formoterol was reduced after 4 weeks of regular treatment.[31,79] In a 12-week study that compared formoterol 12μg or 24μg twice daily with salbutamol and placebo, the response measured as the AUC over time was reduced after 12 weeks for salbutamol and for the higher but not the lower dose of formoterol.[78] The Formoterol and Corticosteroids Establishing Therapy (FACET) study[64] looked at the response to formoterol over 1 year in a 4-way study in which patients were randomised to receive budesonide 400μg or 100μg twice daily with formoterol or placebo. In patients randomised to receive formoterol, morning values for peak expiratory flow rate (PEFR) were higher during the first few days of treatment compared with values measured after the first week. PEFR then remained stable and above values in the placebo group for the remaining 12 months of treatment with formoterol with no deterioration in asthma control. The authors concluded that some tolerance had developed over the first 2–3 days but that this was of little, if any, clinical significance and the major part of the response to formoterol was maintained over the year.

2.1.2 Symptoms, Nocturnal Asthma and Quality of Life

Regular use of salmeterol and formoterol has led to a reduction in both daytime and nocturnal symptoms of asthma in nearly all studies and reduced use

Table II. Controlled studies of ≥4 weeks' duration in adults with asthma in which the clinical response to salmeterol has been compared with the response to placebo or a short-acting β_2-agonist[a]

Study	No. of subjects (no. taking salmeterol)	Duration of salmeterol (wk)	Salmeterol bid dose (μg)	Mean FEV_1 % of predicted	% on ICS	Control group salbutamol (albuterol) dose
Versus placebo						
Dahl et al.[36]	692 (520)	4	12.5, 50, 100	2.29[b]	65	
Cheung et al.[29]	24 (12)	8	50	95	0	
Jones[37]	427 (282)	6	50	2.6[b]	42	
Boyd[38]	119 (55)	12	100	66	100	
Booth et al.[39]	31 (22)	8	50	70	100	
Wilding et al.[40]c	101 XO	26	50	2.71[b]	100	
Nelson et al.[33]	20 XO	4	42	93	33	
Kemp et al.[41]	506 (252)	12	42	63	100	
Lockey et al.[42]	474 (240)	12	42	60	64	
Rosenthal et al.[43]	408 (202)	24	42	84	0	
Kemp et al.[44]	352 (176)	52	50	78	46	
Lemanske et al.[45]c	175 (154)	16	42	73	100	
Lazarus et al.[46]	164 (54)	16	42	93	0	
D'Urzo et al.[47]	911 (455)	24	50	Not given	100	
Versus short-acting β_2-agonist						
Britton et al.[48]	667 (334)	52	50	2.14[b]	63	200μg bid
Beach et al.[49]	20 (10)	6	50	2.9[b]	100	400μg bid
Lundback et al.[50]	388 (190)	52	50	75	64	400μg qid for 3mo, then bid
Castle et al.[51]d	25 180 (14 113)	16	50	Not given	69	200μg qid
Rutten-van Mölken et al.[52]	120 (53)	6	50	59	65	400μg bid
Faurschou et al.[53]	190 (96)	6	100	55	100	400μg qid
Boulet et al.[54]	228 (113)	12	50	66	73	200μg qid
Wenzel et al.[55]	539 (264)	12	42	63	46	180μg qid
Versus short-acting β_2-agonist and placebo						
Pearlman et al.[56]	234 (78)	12	42	67	30	180μg qid
D'Alonzo et al.[57]	322 (106)	12	42	66	22	180μg qid
Juniper et al.[58]	140 XO	4	50	76	74	200μg qid
LeBlanc et al.[59]	367 XO	4	50	77	80	400μg qid
Taylor et al.[60]	165 XO	24	50	80	92	400μg qid
Kemp et al.[61]	451 (149)	12	50	65	43	180μg qid

a The dose of salmeterol is the dose given in the paper (a 50μg dose in the inhaler is equivalent to a 42μg delivered dose).

b Absolute values (litres).

c Corticosteroid reduction included in study design.

d Postmarketing surveillance.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **ICS** = inhaled corticosteroid; **mo** = months; **qid** = four times daily; **wk** = weeks; **XO** = crossover.

of rescue medication.[36-38,42-46,56-60,62-67] This reduction in symptoms has been similar in patients whether or not they were taking an inhaled corticosteroid.

The reduction in nocturnal symptoms has been associated with higher evening peak flow values and a smaller overnight reduction in peak flow,[36,38,56,62,63] as anticipated during drug development. A more detailed study of sleep in patients taking salmeterol 50μg twice daily showed an improvement in sleep quality, with patients spending less time awake or in light sleep and more time in stage 4 sleep.[80]

Regular treatment with both long-acting β_2-agonists has been associated with an improvement in quality of life. Patients taking salmeterol showed an improvement in global scores and scores

Table III. Controlled studies of ≥4 weeks' duration in adults with asthma in which the clinical response to formoterol has been compared with the response to placebo or a short-acting β_2-agonist[a]

Study	No. of subjects (no. taking formoterol)	Duration (wk)	Formoterol bid dose (μg)	Mean FEV_1 % of predicted	% on ICS	Control group salbutamol (albuterol) dose
Versus placebo						
Schreurs et al.[62]	221 (143)	4	6, 12, 24	58	90	
van der Molen et al.[63]	239 (125)	24	24	67	100	
Pauwels et al.[64]	852 (425)	52	12	75	100	
van der Molen et al.[65]	110 (56)	24	24	65	100	
Garcia et al.[66]	19 (10)	4	12	100	32	
O'Byrne et al.[67] Group A	698 (231)	52	4.5	90	100	
O'Byrne et al.[67] Group B	1272 (638)	52	4.5	86	100	
Zetterström et al.[68]	362 (238)	12	9	73	100	
Price et al.[69] Part 1	663 (332)	4	9	NR	67	
Price et al.[69] Part 2	505 (250)	24	9	NR	68	
Versus short-acting β_2-agonist						
Wallin et al.[70]	16 XO	4	24	60	94	400μg bid
Kesten et al.[71]	145 (73)	12	12	2.0[b]	62	200μg qid
Arvidsson et al.[72]	18 (10)	52	12	45	71	200μg bid
Midgren et al.[73]	37 (19)	4	24	73	68	400μg bid
Stålenheim et al.[74]c	99 (42)	12	12	88	55	200μg qid
Thomson et al.[75]c	262 (174)	12	12, 24	57	88	400μg qid
FitzGerald et al.[76]	271 (89)	24	12	79	100	200μg qid
Versus short-acting β_2-agonist and placebo						
Ekström et al.[77]	397 (135)	12	6	62	86	Placebo or terbutaline 500μg qid
Bensch et al.[78]	541 (271)	12	12, 24	66	51	Placebo or salbutamol 200μg qid

a The dose of formoterol is the dose given in the paper (a 6μg dose in the inhaler is equivalent to 4.5μg delivered dose).

b Absolute values in litres.

c Patients in these studies had reversible airways obstruction but not necessarily a diagnosis of asthma.

bid = twice daily; **FEV_1** = forced expiratory volume in 1 second; **ICS** = inhaled corticosteroid; **NR** = not reported; **qid** = four times daily; **wk** = weeks; **XO** = crossover.

for the individual domains of the Asthma Quality of Life Questionnaire compared with placebo.[41,42,58] Regular use of formoterol for 3 months was associated with an improvement in the total score and in the 'activity' and 'symptom' sub-scores of St George's Respiratory Questionnaire.[81] In the FACET study,[64] however, the improvement in the quality of life was only significant when patients took formoterol plus a high dose of budesonide.

2.1.3 Exacerbations

Several small studies have failed to show a reduction in exacerbations in patients taking salmeterol or formoterol, although most had insufficient power to detect this outcome.[37,48,50,56,57,71-73,76] Both drugs have reduced exacerbations in larger studies in which most patients were taking an inhaled corticosteroid. The FACET study was designed specifically to address concerns regarding the effect of long-acting β_2-agonists on exacerbations of asthma. Treatment with formoterol led to a reduction of 26% in severe exacerbations over the year irrespective of whether patients were taking 200μg or 800μg of budesonide daily (figure 1).[64] The effect of quadrupling the dose of budesonide and adding formoterol on the reduction in exacerbation was additive (63%). In a large study of patients with mild asthma by O'Byrne et al.[67] the addition of formoterol reduced the rate of severe exacerbation by 52% in patients taking a low dose of budesonide and was

more effective than doubling the dose of inhaled corticosteroids. In corticosteroid-naive patients in this study, however, treatment with budesonide reduced the risk of severe exacerbations compared with placebo but the addition of formoterol provided no further benefit.

Regular treatment with salmeterol has been associated with a reduction in exacerbations of asthma in two studies in which most patients were taking an inhaled corticosteroid (92%[60] and 64%[42]). A large postmarketing surveillance study reported fewer medical withdrawals due to asthma in patients randomised to salmeterol compared with regular salbutamol.[51] In two studies of patients with asthma who were not taking an inhaled corticosteroid, however, salmeterol did not reduce the number of exacerbations.[45,46]

2.1.4 Exercise-Induced Asthma

Single doses of both salmeterol and formoterol provide marked and prolonged protection against exercise-induced asthma. This protective effect is reduced by approximately 50%, however, when the drugs are taken on a regular basis.[32,33,66]

2.1.5 Effect of Long-Acting β2-Agonist on Need for Inhaled Corticosteroid

Two studies have looked at the effect of a progressive reduction in inhaled corticosteroid dose on markers of inflammation in patients treated with a long-acting β2-agonist. In a crossover study 13 patients taking high doses of an inhaled corticosteroid were given salmeterol 50μg or placebo twice daily in random order; the dose of inhaled corticosteroid was reduced weekly until the drug was discontinued or an exacerbation occurred.[82] Mean inhaled corticosteroid dose was reduced more with salmeterol treatment (87%) than with placebo (69%). Sputum eosinophil counts were higher, however, in the salmeterol group in the week before an exacerbation. The authors concluded that by controlling symptoms salmeterol allowed airway inflammation, as judged by sputum eosinophil counts, to become more advanced.

In a further study, 164 patients taking triamcinolone 400μg twice daily were randomised to continue with the same treatment or change to salmeterol 50μg or placebo twice daily for 16 weeks.[46] Peak flow rates, symptom scores and quality of life were better in patients taking salmeterol or triamcinolone compared with placebo. However, patients treated with salmeterol had more asthma exacerbations and an increase in sputum eosinophil numbers and exhaled nitric oxide levels compared with patients continuing with triamcinolone. These studies show that salmeterol does not reduce inflammation compared with corticosteroids but this may not be apparent clinically because it is still able to relieve symptoms.

A further study, with a rather complicated design, also looked at the effect of corticosteroid withdrawal. In this study it was possible to compare 21 patients randomised to twice-daily treatment with triamcinolone 200μg and salmeterol 50μg with 74 patients randomised to the same dose of triamci-

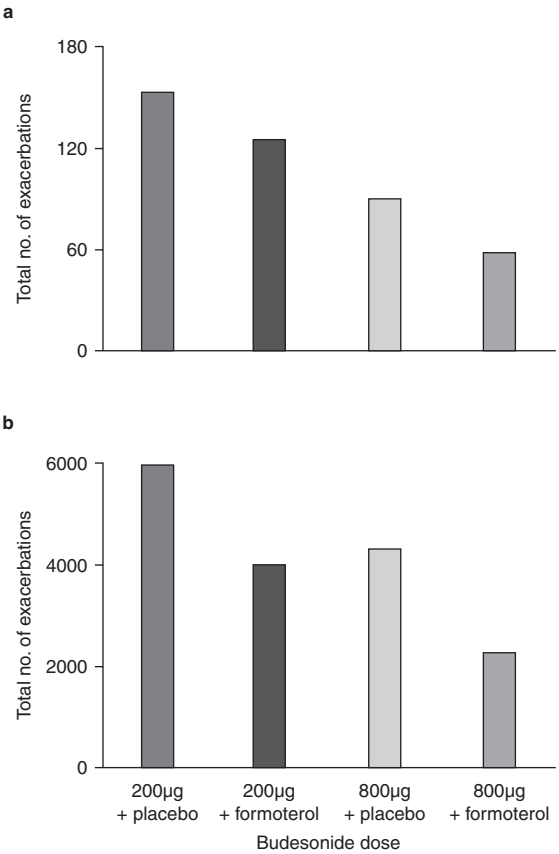

Fig. 1. Total number of severe (**a**) and mild (**b**) exacerbations over 1 year in 852 patients randomised to receive budesonide 100μg or 400μg twice daily with formoterol 12μg twice daily or placebo.[64]

nolone with placebo.[45] There was no difference in the patients' ability to stop triamcinolone completely between the two groups but the number taking salmeterol was small.

A further two studies have looked at corticosteroid reduction rather than cessation. A crossover study by Wilding et al. assessed the effects of adding salmeterol to the dose of inhaled corticosteroid needed to provide adequate asthma control.[40] 101 patients with mild-to-moderate asthma taking at least 200μg beclometasone twice daily were randomised to receive either salmeterol 50μg or placebo twice daily first. Subjects adjusted their inhaled corticosteroid dose according to guidelines, which allowed limited reduction in inhaled corticosteroid dose to a minimum of 200μg beclometasone daily. Salmeterol treatment was associated with a 17% reduction in the dose of inhaled corticosteroid required to maintain good control. There was no difference in exacerbation rate between treatments.

In a large study of 663 patients randomised to budesonide 400μg twice daily with formoterol 12μg or placebo, 505 patients had good asthma control after 4 weeks.[69] These patients were then re-randomised to half the dose of budesonide (400μg daily) with formoterol or placebo for 6 months. Use of formoterol was associated with more rapid asthma control during the first 4 weeks and fewer mild exacerbations as well as better asthma control in the subsequent 6 months.

Taken together, these studies suggest that the addition of a long-acting β_2-agonist may allow some reduction of inhaled corticosteroid dose without clinical deterioration. Replacing inhaled corticosteroids with a long-acting β_2-agonist, however, is associated with an increase in airway inflammation and in asthma exacerbations.

2.2 Comparison with Other Drugs

2.2.1 Short-Acting β_2-Agonists

Several studies have compared salmeterol or formoterol with short-acting β_2-agonists, usually salbutamol but occasionally terbutaline (table II and table III). Twice-daily use of salmeterol and formoterol has consistently caused a greater increase in morning peak flow, with reduced diurnal variation and an improvement in daytime and nocturnal symptoms when compared with short-acting β_2-agonists.[48,50,54,56,70,71,77,78] Quality of life was improved to a greater extent with both long-acting β_2-agonists than with the short-acting β_2-agonists.[52,55,58,81]

2.2.2 Theophylline

Five studies have compared regular use of salmeterol with individually titrated doses of theophylline; all patients were taking an inhaled or oral corticosteroid.[83-87] Compared with theophylline, salmeterol was associated with a higher morning peak flow, a reduction in nocturnal awakenings, a reduction in the need for rescue salbutamol in most studies and with fewer adverse effects.[84-87] In a small study, peak flow did not improve with salmeterol, although salmeterol led to better sleep quality and fewer nocturnal arousals.[83]

In a small 3-month study in patients with moderately severe asthma taking an inhaled corticosteroid the addition of formoterol caused a reduction in diurnal variation in peak flow and improved symptom control at the end of the first month compared with the addition of sustained-release theophylline, but the effect was not sustained and there was no difference between treatments at the end of 3 months.[88]

2.2.3 Leukotriene Antagonists

Five randomised, controlled, double-blind, double-dummy studies have compared salmeterol 50μg twice daily to a leukotriene receptor antagonist in asthma control.[89-93] A 4-week study in patients, most of whom were receiving an inhaled corticosteroid, found that salmeterol 50μg twice daily provided greater improvement in lung function and symptom control than oral zafirlukast 20mg twice daily.[89]

In three 12-week studies[90-92] in 2320 patients who were symptomatic despite using an inhaled corticosteroid, the addition of salmeterol 50μg twice daily improved lung function and provided better asthma control than montelukast 10mg once daily.

A year long study in 1490 patients taking fluticasone propionate compared salmeterol 50μg twice daily with montelukast 10mg in the evening, looking particularly at exacerbation rate.[93] This did not differ between the two groups, nor did symptom control or quality of life, although pre-treatment

FEV_1, and PEFR were slightly higher in the salmeterol group. In four of the five studies[89,91-93] fewer patients in the salmeterol group experienced an asthma exacerbation, although this finding was significant in only two of the studies.[91,92]

In two 8-week studies of patients with exercise-induced asthma, montelukast provided similar protection against an exercise challenge as salmeterol at the start of the study but superior protection after 4 and 8 weeks of treatment due to the development of tolerance with salmeterol.[94,95] Most of the patients were not taking an inhaled corticosteroid.

A small 3-month study[88] with 20 patients in each arm compared the addition of formoterol 9μg twice daily or zafirlukast 20mg twice daily in patients with inadequately controlled asthma despite inhaled corticosteroids. Although formoterol was generally superior to zafirlukast in improving lung function and reducing symptoms, this was not significant at all times.

In summary, long-acting bronchodilators have generally caused a greater improvement in lung function over time and a trend at least towards better asthma control than the leukotriene antagonists. The latter was not seen in the longest and largest study comparing salmeterol and montelukast. Differences in outcome are difficult to interpret without a placebo limb to assess the magnitude of the response to either drug.

2.2.4 Inhaled Corticosteroids

Several studies have compared the addition of a long-acting β2-agonist with an increased dose of an inhaled corticosteroid. In a meta-analysis of nine studies in patients inadequately controlled on an inhaled corticosteroid, the addition of salmeterol was associated with a reduction in exacerbations when compared with at least a doubling of the dose of inhaled corticosteroid.[96] The addition of formoterol 12μg twice daily for 12 weeks was associated with increased morning and evening peak flow, reduced rescue medication use and improved symptom control in 132 patients compared with doubling the dose of inhaled corticosteroids.[97] There was no significant difference in exacerbations requiring oral corticosteroids.

2.3 Use of Long-Acting β2-Agonists for Acute Symptoms

Since formoterol has a rapid onset of action, similar to that of salbutamol and terbutaline, its use as a relief medication and to treat acute asthma has been explored. Salmeterol has a slower onset of action but because it has a long duration of action its use in patients with acute asthma has been studied.

2.3.1 For Use as Required

In a 3-month study, 360 patients who were using at least four puffs of a short-acting β2-agonist a day for asthma relief despite taking an inhaled corticosteroid, were randomised to take terbutaline 500μg or formoterol 6μg when necessary as relief medication. Time to the first exacerbation was increased in those allocated formoterol and no safety issues were identified.[98] In a second study, patients taking formoterol 12μg twice daily on a regular basis were randomised to take further formoterol 6μg or terbutaline 500μg as their relief medication.[99] There was no difference in asthma control between the two treatment groups.

A large 6-month open-label study in 18 124 patients with asthma compared formoterol 6μg by Turbuhaler® [1] and salbutamol 200μg by metered-dose inhaler (MDI), for use for symptom relief.[100] The study was primarily designed to assess safety (see sections 4.1 and 4.2) but efficacy was also assessed. Formoterol was associated with a reduction in the time to first exacerbation and in severe exacerbations compared with salbutamol (14% and 12%, respectively) and a reduction in the number of symptomatic days.

2.3.2 Treatment of Acute Asthma

Salmeterol 100μg twice daily was added to the standard treatment in patients admitted to hospital with acute asthma. No safety issues were identified and 48 hours after the start of the treatment FEV_1 was higher in the salmeterol group compared with the placebo group.[101] In a further study in 19 patients recovering from acute severe asthma, salmeterol 100μg twice daily was more effective than salbutamol 400μg given six times a day in reducing the overnight fall in PEFR.[102]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Two studies have compared the use of formoterol with a short-acting β_2-agonist in patients presenting to the emergency unit with an acute exacerbation of asthma. Formoterol 90μg was compared with terbutaline 10mg, both given by Turbuhaler®,[103] and formoterol 72μg given by Turbuhaler® compared with salbutamol 2400μg given by MDI plus spacer.[104] Formoterol was at least as effective as the short-acting β_2-agonist in both studies.

2.4 Effect of Different Doses of Salmeterol and Formoterol

Three studies have compared the response to different doses of salmeterol,[36,105,106] of which two found a dose-related increase in lung function. Overall asthma control was better with 50μg and 100μg twice daily than with 12.5μg twice daily.[36] Although there was no difference in the response to salmeterol 50μg and 100μg in patients with mild or moderate asthma,[36,106] the higher dose was better in patients with moderate to severe asthma (FEV_1 <50% predicted) in improving morning and evening peak flow and reducing daytime but not night-time symptoms.[105] All studies reported a higher incidence of pharmacologically predictable adverse events with salmeterol 100μg compared with 50μg twice daily and on balance 50μg appeared to be the preferred dose for most patients.

Two studies compared the response to different doses of formoterol. The first study compared formoterol 6μg, 12μg and 24μg twice daily by Turbuhaler® and found a dose-related increase in lung function and in symptom control.[62] There was a higher incidence of pharmacologically predictable adverse events with higher doses.[62] The second study found that formoterol 24μg twice daily led to a greater increase in FEV_1 than formoterol 12μg on the first study day, but this difference had disappeared at the end of 12 weeks and there was no difference in measures of asthma control between the two doses.[78]

2.5 Direct Comparison of Formoterol and Salmeterol

Four studies have compared formoterol and salmeterol directly,[107-110] all comparing twice-daily treatment with formoterol 12μg against salmeterol 50μg (table IV). There was no difference between the two drugs for morning pre-dose peak flow, FEV_1, symptom control or use of rescue medication in any study irrespective of the inhaler used.

3. Efficacy of Long-Acting β_2-Agonists in Patients with Chronic Obstructive Pulmonary Disease

Fewer studies have looked at the longer-term effects of long-acting β_2-agonists in patients with COPD compared with patients with asthma and the results have been less consistent. Patients with COPD have less capacity to respond to any pharmacological intervention and larger studies are needed to show unequivocal changes for relevant outcomes.

Studies comparing long-acting β_2-agonists with placebo, muscarinic receptor antagonists and oral theophyllines, and of more than 4 weeks' duration, are detailed in table V.[111-131] The studies have in-

Table IV. Studies comparing salmeterol and formoterol in patients with asthma

Study	No. of subjects	Duration (wk)	Drug, twice-daily dose (μg) and inhaler type	Placebo arm	% on ICS
Vervloet et al.[107]a	482	24	F 12 Ae S 50	No	100
Campbell et al.[108]b	469	8	F 12 T S 50 A/pMDI	No	100
Condemi[109]a	528	24	F 12 Ae S 50 D	No	100
Nightingale et al.[110]b	42	4	F 12 Ae S 50 D	Yes	100

a Open label.

b Parallel group study followed by a 4-week crossover study.

A = Accuhaler®; **Ae** = Aerolizer®; **D** = Diskus®; **F** = formoterol; **ICS** = inhaled corticosteroid; **pMDI** = pressurised metered-dose inhaler; **S** = salmeterol; **T** = Turbuhaler®; **wk** = weeks.

volved between 29 and 1465 subjects and have lasted up to 1 year.

All 13 studies of salmeterol (presented in 15 papers[111-116,118,120,122-124,126,128-130]) have looked at the 50μg twice daily dose and one of the studies (two papers[113,114]) also looked at the 100μg twice daily dose. Of the six studies of formoterol, five have looked at 12μg twice daily,[117,119,121,125,131] four at 24μg twice daily[117,125,127,131] and one at 6μg twice daily.[117] The main findings in these studies can be summarised as follows.

3.1 Studies Comparing Long-Acting β2-Agonists with Placebo

3.1.1 Lung Function

Salmeterol and formoterol when taken twice daily have been shown to cause bronchodilatation in patients with COPD when compared with placebo. There is usually an increase in pre-treatment morning peak flow,[111,116,118-120,124-128,131] pre-treatment morning FEV_1[113,117,118,120,121,124,126-128,131] and FEV_1 12 hours after drug administration.[122,125] Four studies found salmeterol or formoterol to be more effective than placebo at increasing evening peak flow,[119,124,127,128] whilst two found no difference.[111,116] The increase in morning PEFR has been marginally greater than the increase in evening PEFR.

In the study in which salmeterol 50μg and 100μg were included, the bronchodilator response to both doses was greater than the response to placebo but there was no difference between the two doses.[113] In the three studies comparing formoterol 12μg and 24μg there was also no difference in change in FEV_1 or PEFR between the two doses, although again both doses differed from placebo.[117,125,131] The response to the formoterol 6μg dose produced a similar response to the other two doses in the study by Aalbers et al.[117]

3.1.2 Symptoms and Quality of Life

Twice-daily treatment with salmeterol and formoterol has reduced rescue medication use[111,113,118-122,124-128,131] and most studies have shown a beneficial effect on daytime or nocturnal symptoms compared with placebo.[111,113,117,121,122,124,125,127] In the three studies[117,125,131] comparing formoterol 12μg and 24μg with placebo, symptom scores were lower with both doses of formoterol compared with placebo, although this was not significant in one study[131] and was only significant for the 24μg dose in another.[117] The reduction in symptom scores for the 12μg and 24μg doses were almost identical in two of the studies, whereas in the third, which included the 6μg dose, there was a dose-related reduction in symptom-free days.[117]

Salmeterol and formoterol have generally shown a trend towards a beneficial effect on quality of life compared with placebo, irrespective of the tool used to measure quality of life. The beneficial effects have not always reached the level considered to be clinically important, however, and have not always been statistically significant. Of the eight studies comparing quality of life after administration of salmeterol 50μg twice daily or placebo, two showed a significant improvement with salmeterol,[114,122] five showed an improvement that was not statistically significant[116,118,120,126,128] and one study showed no difference.[123]

Five studies have looked at the effect of formoterol on quality of life. In the two that included the 12μg and 24μg twice-daily doses, both showed an improved quality of life compared with placebo, although the greater benefit was seen with the lower 12μg dose in one study,[125] and with the higher dose in the other.[131] Quality of life did not differ between the 24μg twice daily dose and placebo in a third smaller study,[127] while in the final two studies[119,121] the 12μg twice-daily dose was superior to placebo, although the significance was only stated for one.[121]

3.1.3 Effect on Exacerbations

The effect of salmeterol on exacerbations of COPD has been assessed in some of the larger studies. Salmeterol 50μg twice daily increased the time to first exacerbation in one study[122] and reduced the exacerbation rate in another[120] (1.3 versus 1.04 exacerbations per patient per year for placebo and salmeterol, respectively). It did not cause a significant reduction in exacerbation rates in the other five studies, however,[113,116,124,126,128] and, although the trend was in favour of salmeterol in all the studies, the differences were small.

Table V. Controlled studies of ≥4 weeks' duration in adults with chronic obstructive pulmonary disease (COPD) in which the clinical response to salmeterol or formoterol was compared with placebo or other bronchodilators

Study	No. of subjects (no. on LAβA)	Duration of LAβA (wk)	LAβA bid dose (μg)	Mean FEV_1 % predicted	% on ICS (% on OCS)	Control group
Versus placebo						
Ulrik[111]	66 XO	4	S 50	45	0	Placebo
Grove et al.[112]	29 XO	4	S 50	42	83	Placebo
Boyd et al.[113]	674 (447)	16	S 50 and 100	46	60 (5)	Placebo
Jones and Bosh[114]	283 (188)	16	S 50 and 100	46	71 (16)	Placebo
Weiner et al.[115]	30 (24)	6	S 50	33	NR	Placebo
Chapman et al.[116]	408 (201)	24	S 50	45	61	Placebo
Aalbers et al.[117]	692 (430)	12	F 4.5, 9 and 18	54	NR	Placebo
Mahler et al.[118]	691 (160)	24	S 50	41	25	Placebo FP 500μg bid FP 500μg plus S 50 bid
Szafranski et al.[119]	812 (201)	52	F 9	36	26	Placebo BUD 400μg bid BUD 320μg plus F 9 bid
Calverley et al.[120]	1465 (372)	52	S 50	45	51	Placebo FP 500μg bid FP 500μg plus S 50 bid
Calverley et al.[121]	1022 (255)	52	F 9	36	48	Placebo BUD 400μg bid BUD 320μg plus F 9 bid
Versus ipratropium bromide or tiotropium bromide and placebo						
Mahler et al.[122]	411 (135)	12	S 42	40	NR	Placebo, IB 36μg qid
Rutten-van Mölken et al.[123]	144 (47 S) [47 S+IB]	12	S 50	44	77	Placebo, S 50 + IB 40μg qid
Van Noord et al.[124]	144 (47 S) [47 S+IB]	12	S 50	44	77 (8)	Placebo, S 50 + IB 40μg qid
Dahl et al.[125]	780 (386)	12	F 12 and 24	45	52	Placebo, IB 40μg qid
Rennard et al.[126]	405 (132)	12	S 42	1.27L[a]	NR	Placebo, IB 36μg qid
Wadbo et al.[127]	183 (61)	12	F 18	33	71	Placebo, IB 80μg tid
Donohue et al.[128]	623 (213)	26	S 50	40	66 (5)	Placebo, TB 18μg od
Versus theophylline						
Di Lorenzo et al.[129]	178 open label (91)	52	S 50	2L[a]	17	T bid
ZuWallack et al.[130]	943 open label (313 S+T) [310 S]	12	S 42	41	37 (13)	S 42 + T bid, T bid
Rossi et al.[131]	854 (425)	52	F 12 and 24	47	47	Placebo, T bid

a Mean FEV_1 (% predicted not given).

bid = twice daily; **BUD** = budesonide; **F** = formoterol; **FEV_1** = forced expiratory volume in 1 second; **FP** = fluticasone propionate; **IB** = ipratropium bromide; **ICS** = inhaled corticosteroid; **LAβA** = long-acting β_2-agonist; **NR** = not reported; **OCS** = oral corticosteroid; **od** = once daily; **qid** = four times daily; **S** = salmeterol; **T** = theophylline; **TB** = tiotropium bromide; **tid** = three times daily; **wk** = weeks; **XO** = crossover.

The effect of formoterol on exacerbations has also been rather variable. Formoterol 12μg and 24μg reduced mild exacerbations and the 24μg dose reduced more severe exacerbations in one study.[131] However, neither the frequency of exacerbations nor use of additional therapy for exacerbations was reduced by twice daily treatment with either dose in a second study[125] or by the 12μg dose in a further two studies.[119,121]

3.1.4 Exercise Tolerance and Respiratory Muscle Strength

When compared with placebo, twice-daily salmeterol 50μg reduced Borg scores for perceived exertion in a 4-week study[112] and breathlessness scores in a 16-week study,[113] although the 6-minute walk distance was unchanged in both studies.

When respiratory muscle strength and endurance were studied there was no change after 6 weeks' treatment with salmeterol 50μg twice daily compared with placebo.[115]

3.2 Comparison with Other Bronchodilators

3.2.1 Short-Acting β2-Agonists

The only comparison of short- and long-acting β2-agonists in patients with COPD is a 3-week study in which all patients were taking ipratropium bromide 40μg four times daily.[132] The addition of formoterol 12μg twice daily caused a greater improvement in the FEV_1 over 6 hours, pre-treatment FEV_1, symptoms scores and the symptoms component of the St George's Respiratory Questionnaire compared with the addition of salbutamol 200μg four times daily.

3.2.2 Muscarinic Receptor Antagonists

Three studies have compared ipratropium bromide 40μg four times daily with recommended doses of formoterol and salmeterol[122,125,126] and, although differences were not always statistically significant, the benefit has generally been in favour of the long-acting β2-agonist. In a 12-week study in which formoterol 12μg and 24μg twice daily were compared with ipratropium bromide 40μg administered every 6 hours, both doses of formoterol were more effective at increasing pre-treatment morning PEFR, increasing the FEV_1 over 12 hours and reducing symptoms, rescue medication use and improving quality of life.[125] Two studies comparing salmeterol 50μg twice daily and ipratropium bromide 40μg four times daily did not show any difference in morning FEV_1 or FEV_1 over 12 hours at the end of the studies,[122,126] but salmeterol was associated with a reduction in nocturnal breathlessness and increased time to first exacerbation in one study.[122]

When formoterol 12μg twice daily was compared with a higher dose of ipratropium bromide (80μg three times daily) there were no differences in spirometric outcomes, symptoms or overall quality of life.[127]

A large study has compared salmeterol with once-daily tiotropium bromide in 623 patients. Tiotropium bromide 18μg daily was more effective than salmeterol 50μg twice daily at increasing pre-treatment morning FEV_1, mean FEV_1 over 12 hours (measured as AUC) and evening PEFR. This was in part due to a greater initial response to tiotropium bromide and in part because the bronchodilator response to salmeterol fell over the course of the study, whereas the response to tiotropium bromide was maintained.[128,133] The development of tolerance to the bronchodilating effect of salmeterol has not been seen in other studies in COPD, nor in asthma and requires confirmation. Tiotropium bromide also caused a greater improvement in the St George's Respiratory Questionnaire total score and in the number of patients achieving a 4-point change in score, although only the latter differed significantly from the finding with salmeterol.[128]

3.2.3 Theophylline

Three studies have compared a long-acting β2-agonist with individually titrated oral theophylline, one with formoterol 12μg and 24μg twice daily[131] and two with salmeterol 50μg twice daily.[129,130] For most endpoints the long-acting β2-agonists were superior to theophylline, although not all differences were statistically significant. Significant differences in favour of the long-acting β2-agonist in at least one of the studies included morning PEFR and the 12-hour change in FEV_1,[131] pre-treatment morning FEV_1, symptoms and rescue medication use,[129] number of 'bad days' experienced[131] and satisfaction with treatment.[130] No consistent differences in quality of life measures were seen after long-term treatment with salmeterol or formoterol compared with theophylline despite

the increased adverse events seen with theophylline.[129-131] Whether this is due to increased withdrawals with theophylline is unclear.

3.3 Effect of Adding Long-Acting β_2-Agonists to Other Bronchodilators

Combining salmeterol 50μg twice daily with ipratropium bromide 40μg four times daily increased lung function (FEV_1, airway conductance and evening PEFR) more than salmeterol alone, although the combination was no more effective than salmeterol alone at improving symptoms, rescue medication use, morning PEFR or exacerbation rate.[124] The combination of ipratropium bromide and salmeterol caused a greater improvement in certain quality of life measures, namely the total score, emotional domain and proportion of patients improving by four points considered to be clinically useful on the Chronic Respiratory Questionnaire, and the symptoms component but not total score of the St George's Respiratory Questionnaire.[123]

When combined with orally titrated doses of theophylline, salmeterol caused greater bronchodilatation than was seen with either drug alone, with improved dyspnoea scores and salbutamol-free days. Other outcomes favoured the combinations, although there was no difference in the rate of exacerbation between salmeterol and combined treatment.[130]

3.4 Effect of Different Doses

No consistent bronchodilator dose response effects have been seen with formoterol doses in the range of 6–24μg twice daily,[117,125,131] although the lower dose was more effective among patients with more reversible airflow obstruction in the study by Rossi et al.[131] The effect on symptom scores has also been broadly similar when formoterol 12μg and 24μg doses have been compared. There was, however, a dose-response effect for reduction in symptom-free days for the three doses of formoterol[117] but no differences between doses for the 6-minute walking distance, rescue medication use or exacerbation rates.[117,125,131] Formoterol 12μg and 24μg twice daily produced similar changes in quality of life in one study,[131] while the lower dose caused greater improvements in the total score and all three domains of the St George's Respiratory Questionnaire in another.[125]

For salmeterol, no difference was seen between the 50μg and 100μg twice-daily doses in terms of effect on FEV_1, symptom scores, rescue medication use or exacerbation rates.[113] For several endpoints the lower 50μg dose had the greater effect, including reduction in breathlessness score at the end of a 6-minute walk, total score and impacts component of the St George's Respiratory Questionnaire. In the short form health survey (SF-36), the lower dose of salmeterol improved health score in four of the eight components while the higher dose caused a deterioration in these components.[113,114]

Thus, neither drug has shown a bronchodilator dose-response effect in patients with COPD. The finding that lower doses caused a greater improvement in quality of life than higher doses in some studies (figure 2) is interesting and presumably relates to the balance between the relatively small bronchodilator effect in these patients and increased adverse effects with the higher doses. A similar phenomenon was observed in a study of increasing doses of salbutamol ranging from 400μg to 4mg in patients with COPD.[134] In this study there was a dose-related increase in PEFR and FEV_1, but the incremental effects were small and higher doses were associated with a progressive increase in heart rate and tremor and a fall in oxygen saturation. Patients preferred the middle dose (1mg) where

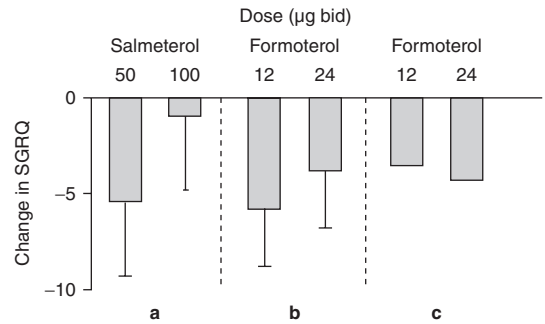

Fig. 2. Change in quality of life (St George's Respiratory Questionnaire [SGRQ] total score) in studies in patients with chronic obstructive pulmonary disease (COPD) that have compared two doses of salmeterol (50μg and 100μg twice daily [bid]) or formoterol (12μg and 24μg bid). Data obtained from the following studies: (**a**) Jones and Bosh;[114] (**b**) Dahl et al.;[125] and (**c**) Rossi et al.[131] after subtracting the response to placebo. In two of the studies the lower dose of β_2-agonist had the greater effect.

presumably the benefits from bronchodilatation were not outweighed by excessive adverse effects. The fact that the quality of life measures favoured the lower dose of the long-acting β2-agonist suggests that this dose achieves the optimum balance between beneficial and adverse effects.

4. Safety of Long-Acting β2-Agonists

The safety of long-acting β2-agonists has been an important consideration following previous concerns about the safety of short-acting β2-agonists. However, assessing their safety is more difficult than assessing their effectiveness. Tremor, palpitations, headache, agitation and muscle cramps are well-recognised adverse effects of all β2-agonists, particularly with higher doses, and this includes the long-acting β2-agonists. Similarly, increasing doses of salmeterol and formoterol cause a progressive increase in heart rate, QTc interval and blood glucose, and a fall in serum potassium in single-dose studies in the laboratory,[34,35] as is also the case with the short-acting β2-agonists. Although systemic response to β2-agonists may show tolerance with regular use, both drugs clearly have the potential to cause systemic adverse effects.[35]

Various approaches have been used to assess adverse events from long-acting β2-agonists and we have considered these under four headings: (i) reports of adverse effects in the studies designed primarily to assess the effectiveness of long-acting β2-agonists; (ii) prospective studies designed to look specifically at safety aspects; (iii) postmarketing surveillance studies; and (iv) population-based studies using case control methods or large databases to relate specific treatments to outcomes such as death.

4.1 Review of Adverse Effects Reported in Prospective Studies of Effectiveness

Most of the prospective studies looking at the effects of salmeterol and formoterol in patients with asthma and COPD have been designed primarily to assess effectiveness. Nevertheless, most of the studies have asked about potential β2-agonist adverse effects such as tremor, palpitations, headache and muscle cramps, and have noted any serious events during the study. Although the predictable adverse effects were noted in most studies, the incidence has not differed significantly from the placebo group in most of the studies looking at formoterol 12μg or salmeterol 50μg twice daily. When higher doses have been included, such as salmeterol 100μg or formoterol 24μg twice daily, the incidence of adverse effects has generally been greater for both patients with COPD[113,114,117,125,131] and with asthma,[36,62,78,80,105,106] as already discussed. For instance, the incidence of tremor in one study was 6% with salmeterol 100μg twice daily compared with <1% with the 50μg twice-daily dose and placebo.[114]

Following submission of data on formoterol to the US FDA, the reviewers looked at asthma exacerbations among patients receiving formoterol 24μg twice daily compared with formoterol 12μg twice-daily or placebo.[135] Although there were no significant differences between the patient groups for total number of asthma exacerbations or for premature withdrawals from the study, there was an increase in severe exacerbations with the higher dose in all three studies (one in children) that had compared the two doses. Information on whether patients were taking an inhaled corticosteroid was unavailable to the authors. As a consequence of these findings, only the 12μg twice-daily dose was approved for marketing in the US.

The studies comparing long-acting β2-agonists with theophylline have shown more adverse effects with theophylline, particularly gastrointestinal adverse effects, palpitations and tachycardia.[83-87,129-131]

ECG monitoring, when it has been carried out in these studies, has not identified a significant difference in dysrhythmias or tachycardia between the long-acting β2-agonists and placebo, although occasional patients have developed dysrhythmias after starting a long-acting β2-agonist.[117,125,126,136] Whether this is due to chance or to the long-acting β2-agonist is difficult to say. A meta-analysis of seven studies of salmeterol 50μg twice daily covering 1443 patients with COPD found no difference in cardiovascular events or deaths compared with placebo, even when patients were stratified by age >65 years or known cardiovascular disease.[137] In this study a serious cardiovascular adverse event occurred in 38 patients (2.6%) taking salmeterol and in 27 (1.9%) taking placebo.

4.2 Prospective Studies Designed to Assess Safety of Long-Acting β_2-Agonists

4.2.1 Use of High Doses

Several studies have compared the effects of higher doses of formoterol with those of terbutaline. In a crossover study in patients with asthma, Tötterman et al. compared the effect of formoterol 72μg and terbutaline 6mg given in three divided doses during the day for 3 successive days with a washout period between the two 3-day studies.[136] Subsequently they gave formoterol 120μg and terbutaline 10mg a day in three divided doses, each for 3 days. Terbutaline caused greater changes in heart rate, serum potassium and QTc interval than formoterol, although 10 of the 15 patients had serum potassium values below the reference range following the higher dose of formoterol (and 12 patients with terbutaline). The fall in serum potassium tended to decrease over the 3 days, whereas baseline heart rate increased progressively. One patient developed atrial fibrillation on formoterol.

The two studies that compared the safety of using formoterol on an 'as needed' basis compared with terbutaline in patients with asthma (see section 2.3) included patients who took up to 12 puffs of formoterol 4.5μg daily.[98,99] In the first study[98] the time to first exacerbation was longer in patients randomised to formoterol and, although occasional patients experienced recognised adverse effects such as tremor, these were not increased in the formoterol group. In the second study[99] in which patients took formoterol 9μg twice daily regularly, plus either formoterol or terbutaline as relief medication, there was no difference in adverse effects between the two treatment arms. Difference in adverse events between formoterol and terbutaline tended to favour formoterol in both studies, although most of the differences were not statistically significant.

The recent study comparing the use of formoterol and salbutamol for use 'as needed' found no difference in total adverse events or serious adverse events between the two groups[100] and no difference in the number of deaths (13 and 11, respectively). However, there were significant differences in asthma-related adverse events in favour of formoterol. There were also significant differences in favour of salbutamol and these included some predictable adverse events and discontinuations due to non-serious asthma and non-asthma adverse events. The adverse events that were increased with formoterol included tremor, headache and anxiety. The reason why episodes of asthma caused more discontinuations in patients taking formoterol when they were reduced overall with formoterol is not clear. The differences were only seen in the countries in which salbutamol was given by MDI, suggesting that they may relate to differences in dose equivalence between the different preparations.

These studies of high doses of formoterol confirm that adverse effects are seen with high doses as expected, but overall the evidence suggests that they are no more serious than those seen with equivalent doses of a conventional short-acting β_2-agonist.

4.2.2 Studies of Cardiovascular Effects

A study by Chervinsky et al.,[138] designed to look at cardiovascular safety in more detail, randomised 352 patients with asthma to salmeterol 50μg twice daily or placebo for 1 year. The study found no significant difference in heart rate, QTc interval, ectopic beats or adverse cardiovascular events. There was a small increase in systolic blood pressure and four patients, all on salmeterol, had changes in their ECG. However, patients with an abnormal ECG at rest or on Holter monitoring or with >10 pack-years of smoking were excluded from the study, and the mean age of participants was only 30 years.

This raises an important caveat for many studies of long-acting β_2-agonists in asthma, which is that nearly all are carried out in subjects who are healthy apart from having asthma. Patients with any evidence of cardiovascular disease are excluded so the patients studied are less likely to be at risk of dysrhythmia or severe cardiovascular adverse effects than the general population of patients given long-acting β_2-agonists.

Studies in patients with COPD have been more likely to include patients with cardiac problems, and in the meta-analysis described in section 4.1[137] 40% of the patients had a cardiac problem. A small single-dose study looked specifically at the effect of a long-acting β_2-agonist in patients with COPD who had experienced a previous cardiac dysrhythmia and

Table VI. Data from a postmarketing study comparing salmeterol and salbutamol (albuterol)[51]

	Salmeterol	Salbutamol	p-Value
No. of patients	16 787	8393	
No. of withdrawals due to asthma (%)	489 (2.91)	318 (3.79)	0.0002
No. of withdrawals not due to asthma (%)	906 (5.4)	430 (5.1)	
Total no. of other serious events (%)	351 (2.1)	176 (2.1)	
No. of deaths due to asthma (%)	12 (0.07)	2 (0.02)	0.105
No. of all cause mortality events (%)	54 (0.32)	20 (0.24)	0.25
No. of SAE (%)	668 (4.0)	342 (4.1)	
No. of drug-related SAE (%)	200 (1.19)	97 (1.15)	

SAE = serious adverse events.

hypoxaemia.[139] Formoterol 12μg and 24μg and salmeterol 50μg were compared in 12 patients with continuous electrocardiography. All three doses caused an increase in heart rate and a fall in serum potassium levels. The effects were most marked with the higher dose of formoterol and four of these patients developed paired or multiform ventricular beats.

These studies show that abnormal cardiovascular findings are rare in young patients taking conventional doses of the long-acting β2-agonists but may occur more frequently in patients with previous cardiac problems, particularly when taking higher doses.

4.2.3 Paradoxical Bronchoconstriction

Paradoxical bronchoconstriction has been reported with salmeterol when given by MDI to patients with asthma.[140,141] In a study of 11 850 patients with stable asthma, peak flow was measured before and after two puffs from a MDI that contained salmeterol or one of two dispersants.[142] Forty-three of 3948 patients randomised to salmeterol (1.1%) had a 20% fall in FEV_1 following the inhalation. The figures for the inhalers containing propellants and dispersants were only slightly higher at 1.7% and 1.8%, supporting the view that the bronchoconstriction relates to the 'inert' constituents in the inhaler. The risk of bronchoconstriction increased with age and with lower pre-treatment FEV_1. Formoterol has not been reported to cause paradoxical bronchoconstriction, which may be because its rapid onset of action allows the active drug to counteract such an effect.

4.3 Postmarketing Surveillance Studies

Three postmarketing surveillance studies have looked at the long-term safety of long-acting β2-agonists once they were in general use.[51,143,144] A fourth study has undergone an interim analysis and has not as yet been published in full.[145,146] The first was a 16-week study of 25 180 subjects, of whom two-thirds (16 787) were randomised to salmeterol 50μg twice daily and a third (8393) to salbutamol 200μg four times daily[51] (table VI). Patients taking salmeterol had fewer withdrawals due to asthma than those taking salbutamol (2.9% vs 3.8%). There were, however, 12 deaths in the salmeterol group compared with two in the salbutamol group, a 3-fold increase since twice as many patients received salmeterol, although the difference was not statistically significant. Despite the large number of participants, the study had limited power to detect a difference in mortality between the two treatments.

Two prescription event monitoring studies have evaluated the safety of salmeterol[143] and formoterol.[144] Exposure data were obtained from prescription details supplied by the Prescription Pricing Authority in the UK and outcome data from questionnaires sent to general practitioners approximately 12 months after the first prescription for a patient had been dispensed. The findings are summarised in table VII.

The two studies were similar in design but the salmeterol study was carried out 5 years earlier, was almost three times as large (15 407 versus 5777 subjects) and included more men and more subjects aged >60 years (i.e. 45% compared with 35% in the formoterol study). Nearly two-thirds of the subjects were still using their long-acting β2-agonist at the end of the year in both studies. The incidence of

Table VII. Details of the two prescription event monitoring studies

	Salmeterol[143]	Formoterol[144]
No. of letters sent	28 019	12 643
No. of replies (%)	17 347 (61)	6693 (53)
No. of patients	15 407	5777
Percentage male; mean age (y)	50; 54	44; 52
Usual dose of drug (μg/day)	100	NS
Percentage taking drug at 12 months	63.5	64.8
Common reasons for stopping the treatment	Not effective, hospitalisation, headache, tremor	Not effective, condition improved, non-compliance
No. experiencing lack of effectiveness (%)	749 (13)	1998 (12.9)

NS = not stated.

anticipated adverse events that had been reported to the general practitioner (i.e. malaise, lassitude, tremor, palpitation and cramps) was low in both studies. The authors concluded that salmeterol use was associated with an increase in malaise, lassitude, tremor and palpitations on the basis of an increased incidence of at least 3-fold between reports in the first month compared with the subsequent event rate.[143] Only three patients reported paradoxical bronchoconstriction. The main reasons for discontinuing treatment were lack of efficacy, headache, tremor, and admission to hospital. In the formoterol study headache, tremor, palpitations, cramp and dizziness occurred at least three times as often in the first month of treatment; withdrawals were mainly due to clinical improvement and non-compliance.[144]

In the salmeterol study, 73 subjects died from asthma, more than half of whom (39) were taking salmeterol in the month before death; there were ten deaths due to asthma in the formoterol study. However, the two figures cannot be compared because of the differences in the study populations, and changes in asthma management and the indications for a long-acting β_2-agonist over the 5 years between the two studies.

The fourth postmarketing study was set up at the request of the FDA in 1996, following reports of asthma deaths associated with the use of salmeterol.[145,146] It was a randomised, placebo-controlled, 28-week study designed to determine whether salmeterol might rarely cause serious asthma-related adverse events. The FDA announced in 2003 that an interim analysis suggested that salmeterol may be associated with an increased risk of life-threatening asthma episodes or asthma-related deaths, particularly in certain groups of patients.[145,146] As far as the primary endpoint, respiratory death or ventilatory failure, was concerned the paper noted a trend towards increased incidence with salmeterol, which did not reach statistical significance. After correcting an error in the original analysis, however, differences in asthma-related deaths or life-threatening experiences (36 vs 23) and asthma-related deaths (13 vs 4) were statistically significant.[145] Further analysis suggested that African Americans may be at greater risk. Only 47% of patients were taking an inhaled corticosteroid and, although serious adverse effects appeared more often in these patients, the data are inadequate to determine whether concurrent use of an inhaled corticosteroid protects against the increased risk of a serious adverse event. The study was designed to recruit 60 000 patients but was stopped after 26 000 patients had been entered. Full details have not as yet been published.

Products containing salmeterol in the US now carry a warning that a small but significant increase in episodes of life-threatening asthma and asthma-related deaths was observed in patients taking salmeterol in a recent study.[146] The FDA emphasises, however, that based on available data, the benefits from salmeterol continue to outweigh the potential risks when used according to the instructions.

4.3.1 Effect of Long-Acting β_2-Agonists in Pregnancy

Since randomised trials of new drugs cannot be carried out in pregnant women, information on outcome in pregnancy relies on postmarketing surveillance and reports of adverse events. The outcome of pregnancy was commented on briefly in two of the postmarketing surveillance studies in which 93 pa-

tients had been taking salmeterol[143] and 33 were taking formoterol[144] at the time of conception or during pregnancy. Five of the babies born to women taking formoterol were premature, one of these had pyloric stenosis and one had a fetal heart rate anomaly. Fewer details are given in the salmeterol paper but the only congenital anomaly was one that affected several other family members. The figures are too small to draw conclusions.

4.4 Population-Based Studies Relating Asthma Medication to Outcome

Several studies have used large databases or a case-control design to relate prescriptions of specific asthma medication to outcomes such as death or hospital admissions. Such studies are usually very large, the endpoints such as death or hospital admission are both important and clear cut, and the data reflect the effect of the drugs as used in clinical practice rather than their effect in selected populations. Care is needed in interpreting the studies, however, as the outcome is clearly dependent on asthma severity which is closely related to treatment. Studies have attempted to allow for this by adjusting for asthma severity and by comparing the associations between different classes of drugs used for asthma. Few studies to date have had sufficient patients taking a long-acting β2-agonist to be able to look at the associations with these drugs in detail.

4.4.1 Asthma Deaths

In a study using the General Practice Research Database, Lanes and colleagues[147] found 43 asthma deaths among nearly 100 000 asthmatic patients. There was a strong relation between all drugs and asthma mortality in the unadjusted analysis, as expected. After adjustment for factors relating to asthma severity, the relative risks for most drugs fell but that for short-acting β2-agonist use and asthma mortality remained high, the relative risk being 51 for patients using more than 13 inhalers of a short-acting β2-agonist a year. The relative risk for long-acting β2-agonists was increased in the adjusted analysis for patients having more than six prescriptions a year; however, the number of patients was small and the finding was not significant (3.2; 95% CI 0.7, 14).

4.4.2 Near Fatal Attacks

In a case-control study in Wessex, England[148] in 1992, 48 patients admitted to the intensive care unit with asthma were compared with age-matched patients admitted to hospital but not to the intensive care unit. The relative risk of a near fatal attack of asthma in patients prescribed salmeterol was 2.3, but this fell when other markers of severity were included in the analysis. The authors concluded that use of salmeterol at that time was a marker of asthma severity and unlikely to be a cause of a near fatal asthma attack.

5. Conclusions

5.1 Efficacy

- Long-acting β2-agonists clearly have an important role to play in the management of asthma. There is good evidence to show that they improve lung function and quality of life, and reduce symptoms, exacerbations and need for relief medication. The reduction in exacerbations has only been seen in studies in which most or all patients were taking an inhaled corticosteroid.
- Some studies have shown that long-acting β2-agonists can allow the dose of inhaled corticosteroid to be reduced. Whether this would be an aim of treatment would depend on the individual patient's symptoms and asthma control in general.
- Long-acting β2-agonists protect against constrictor stimuli such as exercise in patients with asthma but this protection is reduced, although not lost completely, with both formoterol and salmeterol when used regularly.
- There is also some evidence of tolerance in patients with asthma with respect to the bronchodilator effect of formoterol and to salmeterol in one study in patients with COPD. Long-term studies such as the year long FACET study confirm that most of the bronchodilator effect continues undiminished after the first few days.
- Formoterol has been used as a relief medication for use 'as required' and in this context has been more effective than terbutaline and salbutamol in reducing subsequent exacerbations.

- The long-acting β_2-agonists are more effective in improving asthma control than short-acting β_2-agonists, theophylline and an increased dose of inhaled corticosteroid, and are probably more effective than leukotriene antagonists, although the findings have differed between studies.
- In patients with COPD, the long-acting β_2-agonists are clearly effective, although the evidence of benefit generally requires larger numbers of patients to be statistically significant. Both drugs cause bronchodilatation and a reduction in symptoms and some of the larger studies have shown an improvement in quality of life compared with placebo. Most studies have not shown a significant reduction in exacerbations or appreciable effect on exercise tolerance and any effect on these endpoints must be small.
- In patients with COPD, the long-acting β_2-agonists have been more effective in general than ipratropium bromide and oral theophylline; one study suggests that they may be less effective than tiotropium bromide.
- Most of the large studies reviewed have been sponsored by a pharmaceutical company. In the studies comparing two active drugs, the very close concordance between the outcome and the sponsoring company is notable. This clearly raises concerns about subtle biases inherent in the design of these studies, which make a favourable outcome more likely.

5.2 Safety

- The long-acting β_2-agonists, like all β_2-agonists, cause predictable adverse effects that include headache, tremor, palpitations, muscle cramps, and a propensity to reduce serum potassium concentrations. The incidence of adverse effects is low for doses up to 12μg twice daily for formoterol or 50μg twice daily for salmeterol; when the drugs are given in higher doses the incidence of adverse events has generally been higher.
- The long-acting β_2-agonists have little effect on airway inflammation but, by relieving symptoms, may mask increasing inflammation in patients not taking an inhaled corticosteroid or if the corticosteroid dose is reduced inappropriately. When long-acting β_2-agonists are used long-term in patients taking an inhaled corticosteroid, exacerbations are reduced, suggesting that masking of inflammation is not important in this situation.
- Formoterol has been compared with terbutaline and salbutamol for use as relief medication, and this has involved giving higher doses, up to 72μg a day, to some patients. Although both drugs caused predictable adverse effects in some patients, the frequency was if anything less with formoterol compared with terbutaline, although most of the differences were not statistically significant. These findings are supported by laboratory-based studies in which high doses of formoterol and terbutaline were compared.
- There is some evidence that more serious events can occur, very infrequently, with long-acting β_2-agonists as with short-acting β_2-agonists. These include cardiovascular events or life-threatening asthma episodes. The evidence that long-acting β_2-agonists can rarely cause a serious or even fatal cardiac event or dysrhythmia in patients predisposed to such an event comes from various sources. The drugs clearly have the potential to do so through direct cardiac effects and a reduction in serum potassium, and several studies report individual patients developing atrial or ventricular dysrhythmias after starting a long-acting β_2-agonist.[136,139] Such effects are clearly rare and have not been apparent in most prospective studies, although such studies often exclude the most ill patients and those at greater risk of more serious adverse events. Cardiovascular events are more likely to occur in patients who are vulnerable due to myocardial ischaemia, hypoxaemia, hypokalaemia or concomitant medication, such as theophylline, which also stimulate the myocardium.
- Life-threatening asthma and asthma-related deaths have been related to salmeterol in two postmarketing surveys, and severe asthma exacerbations were related to higher doses of formoterol in the data submitted to the FDA. This appears to conflict with the reduction in asthma exacerbations seen with long-acting β_2-agonists in several prospective studies. Paradoxical bronchoconstriction affecting a small proportion of patients is one possible cause, although this

appears to be mainly a problem with salmeterol given by MDI. Masking of deteriorating asthma by a long-acting β_2-agonist could lead to more severe attacks, particularly if patients were not taking an inhaled corticosteroid, although studies of asthma exacerbations in prospective studies have found no evidence to support this.[60,149] Finally, it is possible that some asthma-related deaths are in fact due to a dysrhythmia, since the more severe the asthma the greater the stress on the myocardium. Most asthma deaths, in the UK at least, occur outside hospital[150] so whether a dysrhythmia is the final event is difficult to establish. The recent interim analysis of the postmarketing study of salmeterol from the FDA suggested that patients taking an inhaled corticosteroid may be less likely to have serious adverse events with salmeterol. This would fit with the apparent lack of effect of long-acting β_2-agonists in reducing exacerbations in patients not taking an inhaled corticosteroid.

- Both beneficial and adverse events with the long-acting β_2-agonists may relate to genetic polymorphisms in the β_2-receptor or promoter regions but there are, as yet, few data to assess this.

6. Balance of Efficacy and Safety

Salmeterol and formoterol have been studied extensively since they came on to the market in the early 1990s, and considerable information is available with respect to their efficacy and adverse effects. Salmeterol 50μg twice daily and formoterol 12μg twice daily are very effective drugs, particularly for patients with asthma. Predictable β_2-agonist adverse effects are seen but are rarely a problem and serious adverse effects are unusual. Adverse effects are more common with higher doses, and these should only be used when there is clear evidence of additional benefit and the patient is not at risk of cardiovascular adverse effects.

When compared with other bronchodilators, the long-acting β_2-agonists have usually been more effective and with no more adverse effects reported in most studies. Both drugs are more effective than short-acting β_2-agonists in asthma and probably in COPD, although this has not been studied specifically. The long-acting β_2-agonists have been more effective than ipratropium bromide in patients with COPD, with no difference in adverse events. More information is needed on the relative merits of tiotropium bromide compared with the long-acting β_2-agonists in these patients. The long-acting β_2-agonists are more efficacious than theophylline in patients with asthma and COPD, and with fewer adverse effects.

There are some remaining questions with respect to the clinical use of long-acting β_2-agonists. More information on their effects in pregnancy would be welcome and their safety in patients with cardiovascular disease merits further study. Their role in acute exacerbations of asthma and the use of formoterol as a relief medication requires further work. Although it is recommended that patients should only take a long-acting β_2-agonist in conjunction with an inhaled corticosteroid, this does not always happen and fewer than half the subjects in the recent postmarketing surveillance study in the US were taking an inhaled corticosteroid. The data available support the current recommendation but further studies are needed to assess whether the benefit/risk balance from long-acting β_2-agonists differs between those who are taking an inhaled corticosteroid and those who are not.

The introduction of long-acting β_2-agonists has been an important therapeutic advance for patients with airways obstruction and those with asthma in particular. On present evidence it would seem sensible in patients with asthma to prescribe them in conjunction with an inhaled corticosteroid, and only to use higher doses (salmeterol >50μg or formoterol >12μg) in patients with asthma or COPD when there is clear benefit from the higher dose and patients are not at particular risk of adverse effects. When higher doses are needed for acute attacks of asthma, formoterol is at least as effective and safe as alternative β_2-agonists.

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