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Formoterol

An Update of its Pharmacological Properties and Therapeutic Efficacy in the Management of Asthma

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Synopsis

Formoterol, a selective β_2-adrenoceptor agonist, produces effective dose-proportional bronchodilation, which persists for up to 12 hours, in patients with reversible obstructive respiratory disease. Bronchodilation is significant within

minutes of inhalation, maximal within 2 hours, and at therapeutic doses is equivalent to that produced by standard doses of traditional β_2-agonists. In single-dose studies comparing the two long-acting β_2-agonists formoterol and salmeterol, significant bronchodilation is achieved more rapidly with formoterol than salmeterol. Duration of bronchodilation is similar with both drugs.

The therapeutic efficacy of inhaled formoterol has been equal to or greater than that of salbutamol (albuterol), fenoterol and terbutaline in both short and long term clinical trials. Formoterol reduces symptoms of nocturnal asthma and reduces the need for rescue medication compared with salbutamol. Recent studies have shown that the addition of inhaled formoterol 12 or 24μg twice daily to existing inhaled corticosteroid regimens improves lung function and reduces asthma symptoms compared with placebo. In one well designed study, the frequency of severe exacerbations of asthma over 12 months was decreased by adding formoterol to existing regimens of inhaled corticosteroids. Tolerance to the bronchodilator response of formoterol has not been observed in long term clinical trials.

Because of its long duration of action, formoterol offers significant therapeutic advantages over shorter-acting β_2-agonists in the treatment of nocturnal and exercise-induced asthma. Formoterol is effective in preventing exercise-induced asthma in adults and children and confers significantly more protection than salbutamol when administered 3 and 12 hours before exercise.

In general, inhaled formoterol is well tolerated. The most commonly reported adverse effects, tremor and palpitations, are those traditionally associated with the use of β_2-agonists. Oral formoterol and high doses of inhaled formoterol are associated with more adverse events than are the recommended doses of 6 to 24μg.

Formoterol is currently recommended for use as an alternative to increasing inhaled steroid dosage in patients whose symptoms are inadequately controlled despite therapy with low to moderate doses of inhaled steroids and intermittent short-acting β_2-agonists, and results of recent studies support therapeutic guidelines. Long term clinical studies comparing formoterol and salmeterol have not yet been published. Further studies to evaluate the earlier use of formoterol in patients with mild to moderate asthma are needed to determine the role and long term safety of formoterol in the management of asthma.

Pharmacodynamic Properties

The long-acting selective β_2-adrenoceptor agonist formoterol elicited dose-proportional bronchodilation in patients with asthma as measured by forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and specific airways conductance (sGaw). As with salbutamol (albuterol), clinical effects of formoterol were detected within 1 minute after inhalation; however, the duration of bronchodilation with formoterol was significantly longer than with salbutamol. The onset of action of formoterol was more rapid than that of salmeterol, but the duration of effect (≈12 hours) was similar for both drugs. Formoterol usually produced maximum bronchodilation within 2 hours of inhalation. Dry powder capsule formulations of formoterol have been equipotent with formoterol administered from a metered-dose inhaler (MDI) in improving pulmonary function. Formoterol has exhibited some anti-inflammatory effects *in vitro*. Formoterol inhibited allergen-induced responses in animals and patients with asthma. In patients with moderate chronic obstructive pulmonary disease (COPD), the onset and duration of action of formoterol 24μg

and salmeterol 50μg were similar. However, the effects of salmeterol persisted longer than those of formoterol in patients with severe COPD.

Oral formoterol produced small dose-related increases in heart rate and decreases in blood pressure but cardiovascular effects were significant only after high doses administered by inhalation. The cardiovascular effects of formoterol and salbutamol were similar, but less than those associated with fenoterol. Rebound bronchial hyperresponsiveness has not been seen after stopping treatment with formoterol. Attenuation of the bronchodilator response, with a concomitant decrease in the density of β_2-receptors on peripheral blood lymphocytes, has been noted after 2 or 4 weeks of formoterol use.

Pharmacokinetic Properties

Formoterol exhibited a biphasic serum concentration after single-dose inhalation of 120μg, with an initial peak of 52 ng/L at 0.25 hours followed by a second peak of 40 ng/L at 1.58 hours. The mean plasma half-life of formoterol has been calculated as 3.4 hours after oral administration and 1.7 to 2.3 hours after inhalation.

Therapeutic Efficacy

The therapeutic efficacy of inhaled and oral formoterol has been demonstrated in both short and long term studies in patients with stable asthma or chronic obstructive airways disease. In studies that provided relevant baseline data, mean FEV_1 was usually 60 to 67% of predicted value. In noncomparative and placebo-controlled trials, formoterol improved symptoms, produced clinically relevant increases in PEF and FEV_1, and reduced the need for rescue medication in patients with asthma. Improvements in lung function and control of asthma symptoms with formoterol were maintained during up to 5 years of treatment; there was no evidence of a reduced bronchodilator response or worsening of asthma control. Long term studies showed no difference in lung function in patients using formoterol with or without concomitant anti-asthma therapy.

Results of comparative trials showed inhaled formoterol to be generally superior to salbutamol in improving lung function and asthma symptoms. In a representative study, formoterol 12μg twice daily was associated with a greater decrease in diurnal variation in pre-bronchodilator PEF (from 56 to 17 L/min) than salbutamol 200μg 4 times daily (from 45 to 42 L/min); morning FEV_1 and PEF were higher with formoterol than with salbutamol, even though salbutamol recipients used more rescue medication. Nocturnal asthma symptoms were better controlled by formoterol than by salbutamol. As with MDIs, dry powder formulations of formoterol were at least as effective as those of salbutamol.

Formoterol 6 or 12μg twice daily via Turbuhaler® (a multidose inspiratory flow-driven dry powder inhalation device) was more effective than terbutaline 500μg 4 times daily at increasing morning and evening PEF and reducing day and night-time symptoms in studies involving more than 600 patients with stable asthma. Formoterol and fenoterol similarly improved lung function, but formoterol was more efficacious in relieving nocturnal asthma. Effects on lung function of formoterol and a combined regimen of fenoterol and ipratropium bromide were similar, but the overall efficacy of formoterol was considered to be better.

A recent well designed double-blind study demonstrated that the addition of inhaled formoterol 12μg twice daily to inhaled budesonide 100 or 400μg twice daily reduced the frequency of severe exacerbation of asthma, improved PEF and symptom control and reduced the need for β_2-agonist rescue medication compared with placebo. Similarly, formoterol 24μg twice daily was more effective than placebo in improving morning PEF and asthma symptom score and reducing

the need for rescue medication when added to existing therapy with inhaled corticosteroids. Initial results from a nonblind study indicate that the addition of formoterol 12μg twice daily to inhaled beclomethasone 250μg twice daily resulted in a significantly greater increase in PEF than doubling the dosage of the inhaled corticosteroid.

In asthma patients receiving regular inhaled corticosteroid therapy, improvement in quality of life after 6 months was slightly greater after the addition of formoterol 12μg twice daily via Aerolizer® inhaler (a single-dose inspiratory flow-driven dry powder inhalation device) compared with salmeterol 50μg twice daily via Diskhaler®, although this difference did not reach statistical significance.

A single dose of formoterol 12μg by inhalation provided significantly greater protection against exercise-induced asthma (EIA) than salbutamol 200 or 400μg when administered 3 to 12 hours before exercise. Postexercise FEV_1 decreased by 9% (median) at 3 hours compared with 17% after salbutamol and by 8 to 11% when formoterol was inhaled 12 hours before exercise. In children, formoterol 12μg conferred about 75% protection against EIA when inhaled 3 hours before exercise, compared with the 46 and 17% protection provided by inhaled salbutamol 400 and 200μg, respectively. Similar results were obtained when dry powder capsule formulations of formoterol and salbutamol were compared in patients with EIA.

In patients with chronic obstructive airways disease, formoterol was more effective in increasing FEV_1 and improving symptoms than fenoterol and salbutamol. These results need to be confirmed in long term studies.

When inhaled via Turbuhaler® significant changes in lung function compared with placebo were elicited by formoterol 6μg twice daily. However, in studies of patients using other dry powder inhalation devices, the duration of action of formoterol 6μg was less than that of formoterol 12 and 24μg.

Tolerability

All formulations of formoterol are well tolerated, with the fewest adverse events associated with inhaled formoterol. The most commonly reported adverse effects with inhaled formoterol have been tremor and palpitation, traditionally associated with the use of β_2-agonists. Headache, muscle cramps, nausea and anxiety have also been reported. In long term studies in adults, the incidence of adverse events associated with inhaled formoterol ranged from 0 to 11%. Clinically significant cardiac or metabolic effects were extremely rare. Higher doses of inhaled formoterol (48μg) increased heart rate and tremor amplitude.

Formoterol has been as well tolerated as terbutaline and salbutamol in short and long term comparative studies. Elderly patients have tolerated formoterol as well as salbutamol, with no significant changes in electrocardiogram tracings, heart rate, blood pressure, or laboratory values with either drug.

Dosage and Administration

The current recommended use for formoterol is as an alternative to increasing inhaled corticosteroid dosage in patients in whom asthma symptoms are not adequately controlled with beclomethasone or budesonide 200 to 800μg daily or fluticasone 100 to 400μg daily and as-required short-acting β_2-agonists. Inhaled formoterol 6 μg twice daily via Turbuhaler®, or 12μg twice daily via Aerolizer®, other dry powder devices or MDI should initially be added to the above regimen, and may be increased to 24μg twice daily if necessary. In Europe, formoterol dosage is expressed as that delivered to the patient, 4.5 to 18μg twice daily, rather than the metered dose of 6 to 24μg twice daily. Formoterol is intended as main-

tenance therapy and is not recommended as rescue treatment for severe exacerbations of asthma. Patients should be advised not to discontinue steroids while on formoterol therapy, although dosage adjustments may be possible.

Formoterol is a β_2-selective adrenoceptor agonist that has a rapid onset of action and maintains a bronchodilatory effect for up to 12 hours. Like other selective β_2-agonists, formoterol has minimal stimulating effects on β_1-adrenoceptors and virtually no effect on α-adrenoceptors. Since publication of the previous review of formoterol in *Drugs*,[1] well established guidelines for the use of long-acting β_2-agonists in the management of asthma have been published. Data from single-dose studies comparing formoterol with another long-acting β_2-agonist, salmeterol, are also available. In addition, new dry powder drug delivery devices have been tested. This review updates earlier information, provides an overview of the pharmacological properties of formoterol and further clarifies the role of the drug in the management of asthma.

1. Pharmacological Properties

1.1 Effects on Pulmonary Function in Patients with Asthma

Dose-response studies have indicated that formoterol produces dose-proportional bronchodilation.[1-3] Inhaled formoterol 48μg increased the peak effect for forced expiratory volume in 1 second (FEV_1) changes and the duration of effect when compared with formoterol 12 and 24μg. However, increases in FEV_1 were similar for formoterol 12 and 24μg.

The effect on pulmonary function of inhaled formoterol administered as dry powder capsules has been comparable to that obtained with a pressurised metered dose inhaler (MDI).[4,5] In a recent, cumulative dose-response study in 12 patients, the bronchodilating effect of dry powder and aerosol formulations of formoterol [measured by FEV_1 and peak expiratory flow (PEF)] was similar. The tolerability of the MDI formulation was better than that of the dry powder capsules.[6]

1.1.1 Comparisons with Salbutamol

In studies reviewed earlier,[1] the effects on pulmonary function of oral or inhaled formoterol compared favourably with those of salbutamol (albuterol), with a significantly longer duration of action for formoterol than salbutamol.[1] More recent data indicate that formoterol 12 and 24μg have a similar bronchodilatory effect and are equivalent to standard doses of salbutamol[7-9] in terms of maximum effect (table I; table II), but the duration

Table I. Lung function in 15 patients with stable asthma after dry powder inhalation of single doses of formoterol or salbutamol[7]

	Formoterol			Salbutamol
	6μg	12μg	24μg	400μg
Mean FEV_1 (L)				
baseline	1.81	1.82	1.77	1.75
peak	2.18	2.28	2.25	2.21
12h	1.68	1.78*	1.89**	1.62
duration of action[a] (h)	9.75	11.37	11.70	6.27
AUC	3.11[†]	3.16[‡]	3.18[‡]	3.06
Mean sGaw (L/kPa • sec)				
3 min	0.61	0.75	0.80[§]	0.69
30 min	0.95	1.05	1.07[§]	1.03

a Median time that FEV_1 was ≥20% of maximum achieved.

Abbreviations and symbols: AUC = area under the curve for FEV_1 changes; FEV_1 = forced expiratory volume in 1 second; sGaw = specific airway conductance. * $p < 0.005$ *vs* salbutamol; ** $p < 0.001$ *vs* salbutamol, placebo and formoterol 6μg; [†] $p < 0.05$ *vs* salbutamol and placebo; [‡] $p < 0.05$ *vs* salbutamol, formoterol 6μg and placebo; [§] $p < 0.05$ *vs* formoterol 6μg.

Table II. Bronchodilatory profile of single doses of formoterol, salmeterol and salbutamol inhaled via an MDI and spacer in a double-blind crossover study in 30 patients with moderate asthma.[14] Increases are percentage above baseline values

Variable	Formoterol 24μg (%)	Salmeterol 50μg (%)	Salbutamol 200μg (%)
Specific airway conductance (baseline value 0.46 L/kPa • sec)			
Mean increase at 1 min	44	<16[a]	44
Maximum increase (time to)	135 (2h)	111 (2-4h)	100 (30 min)
Mean increase at 12h	56	58	NR
Forced expiratory volume in 1 sec (baseline value 1.88L)			
Maximum increase (time to)	27 (2h)	25 (3h)	25 (30 min)
Mean increase at 12h	10	11	NR

a A significant increase over baseline (16%) was not recorded until 3 min after inhalation.

Abbreviation: NR = not reported.

of effect of formoterol is longer than that of salbutamol.

The time between inhalation of formoterol 12 and 24μg via MDI or dry powder capsules and significant bronchodilation is similar to that after inhalation of salbutamol 200 or 400μg[7,8] and shorter than with terbutaline 500μg.[10] One minute after inhalation, formoterol significantly increased specific airway conductance (sGaw),[3,7,8] and produced peak dilation at 30 minutes; values after formoterol 12 and 24μg were similar to those with salbutamol 400μg during the first 30 minutes (table I).[7] Peak FEV_1 values are usually reached within 2 hours of inhalation of formoterol.[4,7,11] Furthermore, the maximum increase in FEV_1 produced by formoterol is equal to or greater than that attained with salbutamol 200μg.[1,8] Studies of respiratory impedance have shown that bronchodilation produced by formoterol affects the central and peripheral airways as opposed to the markedly peripheral effect of salbutamol.[12]

1.1.2 Comparisons with Salmeterol

Several single-dose studies comparing the effects of formoterol with salmeterol on lung function and bronchial reactivity in patients with asthma have been published since 1991. In a recent double-blind, randomised, crossover study, 30 patients with stable, moderately severe asthma were given single doses of salmeterol 50μg or formoterol 24μg via a MDI and spacer, and repeated measurements of FEV_1, forced vital capacity (FVC), airways resistance (Raw) and sGaw were made for up to 12 hours. Formoterol and salmeterol had similar bronchodilatory effects that persisted for at least 12 hours. The onset of action was significantly more rapid with formoterol than with salmeterol, and formoterol achieved greater bronchodilation within the first 2 hours after administration than did salmeterol (table II). Similarly, in a single-dose comparison of formoterol 6, 12 and 24μg via Turbuhaler® (a multidose inspiratory flow-driven dry powder inhalation device) with salmeterol 50μg via Diskhaler® (a dry powder inhalation device), the onset of action (time for FEV_1 to reach ≥15% above baseline) of formoterol 12 and 24μg was faster than that of salmeterol.[13] In this study, it was estimated that a delivered dose of between 4.5 and 9μg of formoterol was as effective as salmeterol 50μg. The area under the curve (AUC) for the change in FEV_1, FVC, sGaw and Raw from baseline was similar with formoterol 50μg and salmeterol 200μg.[14]

In a comparison of formoterol 24μg and salmeterol 50μg in 16 patients with moderate chronic obstructive pulmonary disease (COPD), peak bronchodilation was achieved at 4 hours with formoterol and at 5 hours with salmeterol.[15] In these patients, the duration of effect of both drugs was similar, but in another group of patients with severe COPD[16] the effects of salmeterol persisted longer than those of formoterol. A dose-dependent increase in bronchodilation was observed with formoterol 12, 24 and 36μg, but not with salmeterol 25, 50 and 75μg.[16] The discrepancy in results between the 2 studies was attributed to differences in disease severity in the study populations.[16]

1.2 Effects on Allergic Responses

1.2.1 Studies in Patients with Asthma

Comparisons with Salbutamol

In adults and children, inhaled formoterol 12 and 24μg and salbutamol 200μg provided similar

protection against methacholine-induced bronchoconstriction.[1,17] Protection afforded by formoterol 12 or 24μg lasted for at least 12 hours, whereas protection with salbutamol was no different from that in placebo recipients by 4 hours.[17] In a study of 16 patients salbutamol 400μg and formoterol 12 and 24μg produced similar bronchodilation after methacholine-induced bronchoconstriction. However, the onset of action of formoterol 12μg was slightly slower than that of the other treatments.[18] The duration of protection provided by formoterol 12μg against histamine challenge[19] and by formoterol 24μg against cold air sensitivity[20] was prolonged compared with that provided by salbutamol 200μg.

Both formoterol 30μg and salbutamol 500μg completely inhibited the early asthmatic reaction to allergen challenge in 12 patients with allergic asthma. Although both drugs significantly inhibited the late asthmatic reaction, the mean decrease in PEF was significantly less after treatment with formoterol than with salbutamol.[21] Formoterol 24μg and beclomethasone 200μg similarly reduced both the allergen-induced late asthmatic response and increase in airway responsiveness in 6 patients. Neither drug affected the increases in blood and sputum eosinophils and CD25+ lymphocytes associated with the inflammatory process. Formoterol, unlike beclomethasone, produced bronchodilation in addition to preventing bronchoconstriction.[22]

Comparisons with Salmeterol

Formoterol and salmeterol have performed similarly in studies comparing their bronchoprotective effects. In a dose-finding study in 12 patients, formoterol 12 and 24μg and salmeterol 50 and 100μg were equally effective in protecting against methacholine-induced bronchoconstriction for up to 24 hours.[23] Similarly, formoterol 24μg and salmeterol 50μg conferred comparable protection for at least 16 hours in methacholine provocation tests in 15 patients.[24]

1.3 Cardiovascular Effects

Oral formoterol 20 to 300μg produced dose-related increases in heart rate and decreases in blood pressure in healthy volunteers.[1] The cardiovascular effects of repeated doses of inhaled formoterol 24μg, salbutamol 400μg, and fenoterol 400μg have been studied recently in 12 healthy volunteers. The inotropic, chronotropic, and electrophysiological effects of formoterol were similar to those of salbutamol and less than those of fenoterol. All 3 drugs significantly increased heart rate and the corrected QT interval and decreased total electromechanical systole and diastolic blood pressure. Although the mean maximum cardiovascular and metabolic effects of salbutamol and formoterol were similar, the cardiovascular effects of formoterol lasted longer.[25] In patients with asthma who received single inhalations of formoterol 12, 24, 48, and 96μg as dry powder, significant increases in heart rate and QTc interval and decreases in systolic blood pressure and electromechanical systole were noted only at high doses.[26]

1.4 β_2-Adrenoceptor Expression

In vitro studies have shown that salbutamol, salmeterol and formoterol reduce β_2-adrenoceptor density and β_2-adrenoceptor mRNA expression in human lung tissue.[27] In 8 healthy volunteers, inhaled formoterol 72μg and salmeterol 300μg had equivalent β_2-agonist effects at rest as indicated by increased finger tremor and decreased serum potassium. In states of increased endogenous adrenergic tone and in the presence of fenoterol both drugs exhibited β_2-receptor antagonism.[28]

Newnham et al.[29] have shown attenuation of the peak bronchodilator response and the duration of bronchodilation in a 4-week placebo-controlled study of formoterol 24μg twice daily from a MDI in 7 patients. However, a significant bronchodilator response was still present at 6 hours after the last dose. In accordance with the attenuated bronchodilator response, the density of β_2-receptors on blood lymphocytes was significantly reduced as was the maximal cAMP response to isoprenaline (isoproterenol). The same authors reported similar

results in 16 patients treated with formoterol 24μg twice daily from dry powder capsules.[30]

1.5 Other Effects

In healthy volunteers, repeated inhalation of formoterol 24μg, salbutamol 400μg or fenoterol 400μg caused similar increases in plasma glucose levels, whereas formoterol and fenoterol had a greater hypokalaemic effect than salbutamol.[25] Similar decreases in serum potassium levels have been seen in patients with asthma given cumulative doses of formoterol 12 to 228μg or salbutamol 200 to 3800μg over 6 hours, although there were no clinically important electrocardiographic changes.[26,31] In most patients, however, serum potassium levels, although decreased, remained within the normal range.[1,31] Dose-related decreases in serum potassium levels occurred in patients with asthma who inhaled single doses of formoterol 12, 24, 48 and 96μg, but only changes after the highest dose were considered to be of possible clinical relevance.[26]

In vitro, treatment with formoterol and salmeterol caused a rapid intracellular accumulation of cAMP in a neuroblastoma cell line; intracellular levels quickly decreased after the removal of formoterol, but not salmeterol.[32] Oral and inhaled formoterol significantly increased cAMP levels in healthy volunteers.[1]

Formoterol is a significant ciliostimulant and was 100 times more potent than terbutaline in increasing ciliary beat frequency *in vitro* and *in vivo*. Furthermore, the effect of formoterol lasted twice as long as that of terbutaline.[33] In patients with chronic bronchitis, formoterol significantly increased ciliary beat frequency and the mucociliary clearance rate.[1,34]

1.6 Mechanism of Action

The exact mechanism by which formoterol exerts prolonged effects on lung function in patients with asthma is unknown. The prolonged duration of action of formoterol may be associated with its interaction with membrane lipid bilayers (plasmalemma).[35] It is considered that the plasmalemma lipid layer of airway smooth muscle acts as a depot for β_2-agonists with moderate to high lipophilicity. β_2-Agonists, once having partitioned into the bilayer, remain available to interact with the β_2-adrenoceptor. Formoterol, which is moderately lipophilic, enters the plasmalemma and is retained. The drug is also able to reach the receptor from the aqueous phase, accounting for its rapid onset of action. Subsequently, it gradually leaches out from plasmalemma, continually activating the receptor, imparting a prolonged bronchodilatory effect.[36]

A high concentration of formoterol appears to be necessary to achieve a long duration of action, This may explain why oral formoterol has a shorter bronchodilator effect than the inhaled drug[35] and differences in the effective dose of formoterol when administered via various delivery devices (see section 3.3 and section 5).

2. Overview of Pharmacokinetic Properties

In the previous review of formoterol in *Drugs*,[1] the urinary excretion rate and cumulative urinary excretion were used to calculate an elimination half-life for inhaled formoterol of 1.7 to 2.3 hours. Following inhalation of formoterol 24μg, 24% of the dose is excreted in the urine in 12 hours. After oral (systemic) formoterol 40μg, urinary excretion is 9.6% in 24 hours. After inhalation of formoterol 12, 24, 48 and 96μg as dry powder, the change in ratio of the RR and SS enantiomers in the urine suggested that the inactive SS enantiomer preferentially reaches the systemic circulation after inhalation of the drug.[37]

In early studies, plasma concentrations were often below detectable limits after inhalation of therapeutic doses of formoterol. Braat et al. [38] used high performance liquid chromatography (HPLC) with electrochemical detection to measure plasma concentrations during an 8-hour period after an oral dose of formoterol 168μg. Mean peak concentration (C_{max}) was 70.1 ng/L and half-life was 3.4 hours. C_{max} values of about 160 ng/L have been previously reported after repeated oral doses of 40 to 80μg.[1]

Most pharmacokinetic data in the previous review were obtained from animal studies of oral doses of formoterol.[1] Recently, the pharmacokinetics of a single 120μg dose of inhaled formoterol were studied in healthy volunteers.[39] Inhalation of a single dose of formoterol 120μg appeared to result in a biphasic pattern of kinetics in serum, with an initial C_{max} of 52 ng/L occurring at 0.25 hours. Following a lag period, a second C_{max} of 40 ng/L occurred at 1.58 hours.[39]

3. Therapeutic Efficacy

In early noncomparative and short term comparative trials, formoterol was equal or superior to conventional β_2-agonists in improving lung function and overall asthma control. Since the previous review,[1] several long term, placebo-controlled and comparative trials in adults and children with stable asthma have been conducted.

In most studies, lung function was objectively assessed by measuring FEV_1, PEF and FVC. In studies that provided baseline spirometric data, FEV_1 was generally 60 to 67% of predicted value. In many studies, patients kept diaries of symptoms and morning and evening measurements of PEF. A visual analogue scale (VAS) was used to assess breathing ability, sleep patterns, and general well-being. In most studies of exercise-induced asthma (EIA), a standard exercise test of ≥6 minutes of treadmill running was performed from 3 to 12 hours after an inhaled dose.

3.1 Stable Bronchial Asthma

3.1.1 Short Term Studies

Several early short term, noncomparative trials demonstrated the therapeutic efficacy of oral twice daily formoterol 40 to 80μg in adults and 2 to 6 μg/kg in children, or inhaled formoterol 12μg twice daily in children.[1] In a recent double-blind, crossover trial, involving 43 patients with mild to moderate asthma, the percentage of predicted FEV_1 prior to the next dose in patients receiving formoterol 12μg was superior to that achieved with formoterol 6μg and placebo after 2 weeks of treatment.[40] Administration of formoterol 6, 12 or 24μg twice daily via Turbuhaler® to 156 patients with asthma significantly decreased symptom scores and supplementary medication requirements compared with placebo.[41]

3.1.2 Long Term Studies

Several recent studies, ranging in duration from 12 to 25 months, have demonstrated the long term efficacy of formoterol 12 or 24μg twice daily (table III), confirming earlier results.[1] In 1 study, control of asthma symptoms and improvements in lung function were maintained without an increase in inhaled formoterol dosage or corticosteroid usage for up to 60 months.[42] In this, as in an earlier study,[43] there was no reduction in bronchodilator response to formoterol during 5 years of treatment. Formoterol significantly reduced the need for systemic steroid intervention.[42] Other noncomparative trials,[44-46] involving patients with moderately severe to severe asthma, reported continued control of asthma symptoms with inhaled formoterol 12 or 24μg twice daily over treatment periods of 12 to 20 months. Similarly, in a 12-month trial of formoterol 12 or 24μg twice daily in 280 patients, the beneficial effects of the drug on pulmonary function were maintained throughout the study.[47] Lack of evidence of desensitisation was reported by Maesen et al.[48] in 59 patients who had used formoterol 12μg twice daily alone or concomitantly with other (unstated) anti-asthma drugs for 25 months.

Most early trials of inhaled formoterol in children with asthma were of short duration.[1] A recent 1-year noncomparative trial (available as an abstract) evaluated the efficacy and tolerability of formoterol 12 and 24μg twice daily inhaled as dry powder capsules in 82 children. Measures of lung function (PEF and FEV_1) and clinical efficacy variables (daytime and night-time symptoms, rescue medication requirements and sleep disturbances) steadily improved over the course of the year (table III), without evidence of tachyphylaxis.[49]

3.1.3 Comparisons with Other Bronchodilators

Salbutamol

Earlier studies involving more than 700 patients showed that the overall efficacy of formoterol was

Table III. Lung function in recent long term, noncomparative clinical studies of formoterol (F) in patients with stable asthma

Reference (no. of patients)	Duration of study (regimen)	FEV_1 (L)			PEF (L/min)			Comments
		BL	3mo	12mo	BL	3mo	12mo	
Clauzel et al.[44] (68) (abstract)	20mo (F 24μg bid)	1.65 (PE) 2.25 (PD)		1.91 2.28				Nocturnal symptoms and rescue medication decreased. At 20mo PE FEV_1 was 1.85L and PD value was 2.32L
de Blic & Kuusela[49] (82) (abstract)	12mo (F 12-24μg bid)				255 (MPE)	282	319	Study in children. Other efficacy variables steadily improved
Hock et al.[50] (74) (abstract)	12mo (NR)	2.25		2.45	398 (M) 421 (E)		436 450	Nocturnal symptoms and rescue medication decreased
Kesten et al.[45] (58)[a]	12mo (F 12μg bid)		2.3 (MPE)	2.42		396 (M) 413 (E)	396 420	There was a trend for continued improvement in efficacy
Kesten et al.[45] (54)[b]	9mo (F 12μg bid)	1.88 (MPE)	1.98	2.09	320 (M) 363 (E)	357 380	378 390	Significant improvement of PEF and asthma symptoms after substitution of formoterol for salbutamol
Maesen et al.[48] (59) (abstract)	25mo (F 12μg bid)	1.70 (MPE)	2.0	2.15				At 25mo, FEV_1 was 2.2L. Reversibility was 15% throughout the study
Steffensen et al.[46] (116)	12mo (F 12μg bid)				360 (PE) 430 (PD)	400 440	400 435	Administered as dry powder[c]

a For the first 3mo patients received formoterol 12μg twice daily as part of a double-blind randomised comparison with salbutamol 200μg 4 times daily. Thereafter, patients received formoterol in a 9mo noncomparative trial.

b Patients had been treated with salbutamol 200μg 4 times daily for 3mo before receiving formoterol.

c Aerolizer® inhaler.[51]

Abbeviations: bid = twice daily; BL = baseline; E = evening; FEV_1 = forced expiratory volume in 1 second; M = morning; MPE = morning predose; NR = not reported; PD = postdose; PE = predose; PEF = peak expiratory flow.

equal to or greater than that of salbutamol.[1] These results have been confirmed by more recent results[46,52-58] from comparative studies of formoterol 12 to 24μg twice daily and salbutamol 200 to 400μg 2 to 4 times daily inhaled as aerosol or dry powder capsule formulations (table IV). Patients treated with inhaled formoterol (via MDI) generally required less additional medication, experienced fewer asthma attacks and showed greater improvement in clinical parameters than patients treated with inhaled salbutamol (via MDI). In one crossover study,[53] a preference for formoterol was reinforced over a 1-year follow-up when 5 of 8 patients receiving salbutamol voluntarily changed to formoterol. Mean morning PEF values were significantly higher in patients receiving formoterol (427 *vs* 372 L/min), even though salbutamol recipients used significantly more additional on-demand medication (15.6 *vs* 7.6 puffs/week).[58] Similarly, Midgren et al.[56] reported a 20% increase in morning mean PEF compared with baseline in patients treated with formoterol 24μg twice daily, whereas mean PEF did not increase in patients treated with salbutamol 400μg twice daily. Treatment with formoterol 12μg twice daily was associated with a significantly greater reduction in diurnal variation in pre-bronchodilator PEF (from 56 to 17 L/min) than treatment with salbutamol (from 45 to 42 L/min). The numbers of episodes of asthma and the number of sleep disturbances per week were significantly lower in patients treated with formoterol than in those receiving salbutamol.[54]

An 8-week crossover study in 25 children (available as an abstract)[59] showed that changing from salbutamol 200μg twice daily to formoterol 24μg twice daily significantly improved PEF.

Moreover, significant improvements in PEF obtained in patients who were initially started on 4 weeks of therapy with formoterol were maintained when these patients switched to 4 weeks of therapy with salbutamol.

Formoterol has also been reported to be more effective than salbutamol in comparative studies of dry powder capsule formulations[46,52,55] (table IV). In a study of formoterol 12 or 24μg twice daily versus salbutamol 400μg 4 times daily in 198 elderly patients,[52] both doses of formoterol significantly increased morning PEF compared with salbutamol. In another recent large, double-blind, randomised study of 318 patients,[55] formoterol 12 and 24μg twice daily improved night-time symptoms more than salbutamol 400μg 4 times a day. The authors noted no advantage for formoterol 24μg over formoterol 12μg. Efficacy was maintained in 280 of these patients treated for an additional 12 months with formoterol 12μg.

Terbutaline

Overall efficacy of formoterol 12μg twice daily has been rated as better than that of terbutaline 250 or 500μg 4 times daily in studies involving up to 150 patients.[1] Furthermore, formoterol has been shown to relieve night-time symptoms more effectively than terbutaline.[60]

These findings have been confirmed in a recent randomised, double-blind, parallel group study involving 291 evaluable patients treated with formoterol 12μg twice daily or terbutaline 500μg

Table IV. Summary of recent double-blind, randomised trials comparing inhaled formoterol (F) with salbutamol (S) in patients with bronchial asthma

Reference	Study duration (wk) [formulation]	Dosage (μg) [no. of patients]	FEV_1	PEF	Need for rescue medication	Control of symptoms
Angus & Thomson[52] (abstract)	12 [DPC]	F 12 bid [198 total]		(M) F 12 > S (E) F 12 > S	S > F 24	
		F 24 bid		(M) F 24 > S (E) F 24 > S		
		S 400 qid				
Arvidsson et al.[53]	4 [MDI]	F 12 bid [8]		F ≥ S	S ≥ F	F ≥ S
		S 200 bid [8]				
Kesten et al.[54]	12 [MDI]	F 12 bid [73]	F > S		S > F	F > S
		S 200 qid [72]				
Maesen[55] (abstract)	12 [DPC]	F 12 bid [324 total]	F 12 ≡ S	F 12 ≡ S		F ≥ S
		F 24 bid	F 24 ≡ S	F 24 ≡ S		
		S 400 bid				
Midgren et al.[56]	4 [MDI]	F 24 bid [19]		(M) F > S (E) F > S	S > F	F > S
		S 400 qid [16]				
Sprogoe-Jakobsen et al.[57] (abstract)	6 [MDI]	F 12 bid 20]				(E) F > S
		S 200 bid [18]		F ≥ S	S > F	
Stålenheim et al.[58]	12 [MDI]	F 12 bid [42]	F ≡ S	(M) F > S	S > F	F ≡ S
		S 200 qid [47]				
Steffensen et al.[46]	12 [DPC[a]]	F 12 bid 103]	F ≡ S	F > S, PL	S, PL > F	F > S, PL
		S 400 qid [100]				
		PL [101]				

a Aerolizer® inhaler.[51]

Abbreviations and symbols: bid = twice daily; DPC = dry powder capsules; E = evening; FEV_1 = forced expiratory volume in 1 second; M = morning; MDI = metered-dose inhaler; PEF = peak expiratory flow; PL = placebo; qid = 4 times daily; > indicates a significantly greater effect, need for rescue medication or better symptom control; ≥ indicates a tendency for greater effect, need for rescue medication or symptom control; ≡ indicates similar efficacy.

4 times daily via Turbuhaler® for 12 weeks. Formoterol significantly improved morning and evening PEF and reduced night-time symptoms when compared with terbutaline PEF and placebo. Mean morning PEF increased by 18% with formoterol compared with a slight decrease with terbutaline.[61] Furthermore, in a large double-blind, placebo-controlled, parallel group study of 397 patients, formoterol 6μg twice daily via Turbuhaler® significantly improved morning predrug PEF by 20 L/min compared with a 9 L/min increase with terbutaline 500μg 4 times daily. Daytime and night-time asthma symptom scores also improved significantly more in patients receiving formoterol than in terbutaline recipients.[62]

Other Drugs

Formoterol has been compared with fenoterol and with a combined regimen of fenoterol and ipratropium bromide.[1] Although lung function improved similarly with formoterol 12μg twice or fenoterol 200μg 3 times daily, fenoterol was less effective in treating nocturnal asthma symptoms. Overall efficacy of formoterol was rated better than that of fenoterol. Similarly, overall efficacy of formoterol was rated better than that of the combination of fenoterol and ipratropium bromide, even though bronchodilation was similar in the 2 groups.

3.1.4 Addition to Existing Inhaled Corticosteroid Regimens

Therapeutic guidelines (see section 6) recommend adding a long-acting β_2-agonist to low doses of inhaled corticosteroids in patients with persistent symptoms or less than optimal lung function. Adding inhaled formoterol 24 to 48μg daily to existing regimens of inhaled corticosteroids has now been shown to decrease the frequency of exacerbations of asthma,[63,64] the severity of asthma symptoms[63,64] and the need for short-acting β_2-agonists for symptom relief,[63-65] and to improve PEF.[63-65] Preliminary results suggest that the addition of formoterol to inhaled corticosteroids is at least as effective in improving lung function and controlling asthma symptoms as doubling the dose of inhaled steroids.[65]

A recent double-blind, randomised, parallel group trial conducted by the Formoterol And Corticosteroid Establishing Therapy (FACET) International Study Group[63] assessed the frequency of exacerbations of asthma (primary outcome), severity of symptoms, the need for β_2-agonist rescue medication and PEF in 694 patients treated twice daily with budesonide plus formoterol via Turbuhaler® or placebo. After a 4-week run-in period of treatment with budesonide Turbuhaler® 800μg twice daily, patients received twice daily treatment with budesonide 100μg plus placebo, budesonide 100μg plus formoterol 12μg, budesonide 400μg plus placebo or budesonide 400μg plus formoterol 12μg for 12 months. Patients who initially received daily doses of more than 2000μg of beclomethasone, 1600μg of budesonide by MDI, 800μg of budesonide by Turbuhaler®, or 800μg of fluticasone, were excluded from the study.

The rate of severe exacerbations (requiring treatment with oral glucocorticoids, or a decrease in PEF to <30% below baseline value on 2 consecutive days) was reduced by 26% when formoterol was added to budesonide 100μg, by 49% when budesonide was increased to 400μg and by 63% when formoterol was added to budesonide 400μg (fig. 1). The reduction in the rate of severe exacerbations after increasing the dosage of budesonide from 200 to 800μg daily was greater than that achieved by adding formoterol to the lower dose of budesonide ($p = 0.03$), but these regimens were similarly effective in reducing the rate of mild exacerbations (37 *vs* 40%). The addition of formoterol to either dose of budesonide was associated with a significant improvement in both daytime and night-time symptom scores and reduced the need for rescue medication. In comparison, increasing the dose of budesonide reduced the symptom score only during the day and the need for rescue medication only at night. The increase in PEF was significant when formoterol was added or the dose of inhaled steroid increased, but tended to be greater with the combined regimen.

The effects of adding inhaled formoterol 24μg twice daily (via Turbuhaler®) [n = 107] or placebo (n = 101) to existing therapy with a constant dose

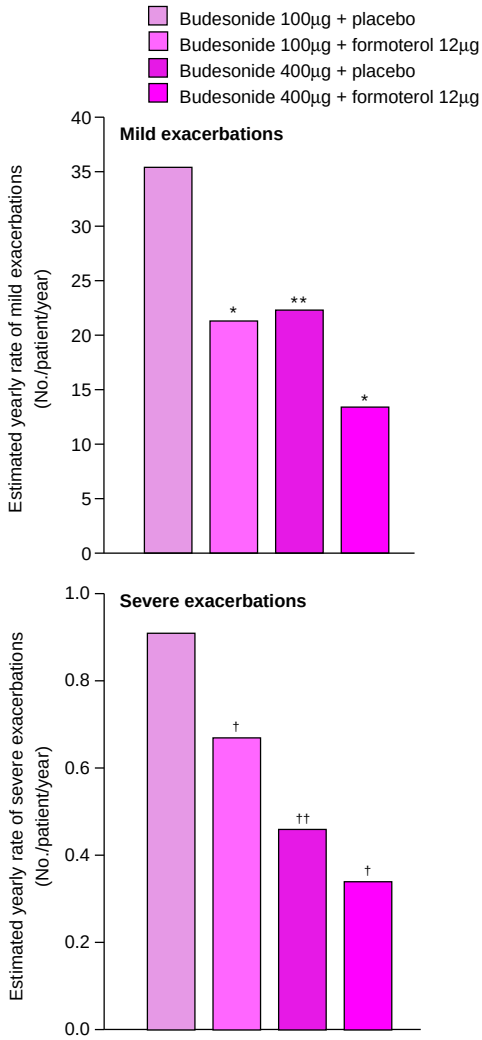

Fig. 1. Frequency of mild and severe exacerbations of asthma in patients treated with inhaled formoterol via Turbuhaler® in addition to inhaled corticosteroids. Estimated yearly rate of mild exacerbations (morning peak expiratory flow that was >20% below the baseline value; the use of >3 additional inhalations of rescue medication per 24 hours compared with baseline; or awakening at night due to asthma) or severe exacerbations (requiring treatment with oral glucocorticoids or a decrease in peak expiratory flow of >30% below baseline on 2 consecutive days) during 12 months' treatment with budesonide 100µg plus placebo (n = 213) or formoterol 12µg (n = 210) twice daily, or budesonide 400µg plus placebo (n = 214) or formoterol 12µg (n = 215) twice daily.[63] *Symbols:* * p < 0.001 formoterol *vs* placebo; ** p < 0.001 higher *vs* lower dose of budesonide; † p < 0.01 formoterol *vs* placebo; †† p < 0.001 higher *vs* lower dose of budesonide.

of inhaled corticosteroids (100 to 3200 µg/day expressed as equivalent doses of different drugs) were compared over a period of 6 months. Inhaled corticosteroid dosage was <800µg daily in 38.5% of patients and >1600µg daily in 18.4% of patients. Treatment with formoterol produced a significantly greater increase in morning PEF (25.9 *vs* –2.1 L/min) and a greater decrease in total asthma symptom score and rescue medication requirements than placebo, which was independent of the dose of inhaled corticosteroid. 33 patients treated with formoterol and 32 treated with placebo required one or more courses of oral prednisolone (58 and 55 courses, respectively) to alleviate exacerbations of asthma.[64]

A randomised, nonblind study compared the effects of adding formoterol 12µg twice daily to existing therapy with beclomethasone 250µg twice daily or increasing the inhaled corticosteroid dosage to 500µg twice daily in 132 patients with asthma.[65] The increase in mean morning PEF and the decreased use of rescue medication was significantly greater in patients given formoterol than in those whose inhaled steroid dosage was doubled (treatment difference of 20.3 L/min).

Quality of life (measured with the St George's Respiratory Questionnaire) was significantly improved in 482 asthma patients 3 and 6 months after the addition of formoterol 12µg twice daily via Aerolizer® inhaler (a single-dose dry powder capsule inhaler) or salmeterol 50µg twice daily via Diskhaler® to regular inhaled corticosteroid therapy. The improvement was slightly greater in formoterol compared with salmeterol recipients, although this difference did not reach statistical significance.[66]

3.2 Exercise-Induced Asthma

Exercise is a frequent trigger for asthma exacerbation. In fact, EIA may occur in up to 90% of patients with asthma.[67]

As reported in the previous review,[1] a single dose of formoterol 24µg provided prophylaxis against EIA when inhaled up to 8 hours before vigorous exercise. Formoterol 24µg and fenoterol 400µg were equipotent in preventing EIA when

Table V. Summary of placebo-controlled crossover trials of formoterol (F) and salbutamol (S) in patients with exercise-induced asthma

Reference	No. of patients [age (y)]	Formulation	Dose (μg)	Mean percentage decrease in exercise FEV_1 or PEF[a]	Overall efficacy[b]
Boner et al.[67]	15 [9.6]	MDI	F 12	7.7	3h: F > S ≡ PL
			S 200	21	12h: F > S ≡ PL
			PL	22	
Daugbjerg et al.[68]	16 [12.4]	DPC[c]	F 12	11	3h: F > S > PL
			S 400	26	12h: F > S ≡ PL
			PL	35	
Henriksen et al.[69]	12 [12.6]	MDI	F 12	10	0.5h: F + S > PL
			S 200	40	3h: F > S ≡ PL
			PL	47	5.5h: F > S ≡ PL
					8h: F > S ≡ PL
Patessio et al.[70]	12 [25.6]	MDI	F 12	10[d]	2h: F ≡ S > PL
			S 200	20[d]	8h: F > S ≡ PL
			PL	33[d]	8h: F > S ≡ PL

a Measured after second exercise test.

b Efficacy was assessed by measuring FEV_1 at 1, 3, 5, 10, 15, 20, 30 and, in some instances, 60 min after treadmill exercise. Exercise tests were performed at the times shown after single-dose inhalation of each drug.

c Aerolizer® inhaler.[51]

d Values estimated from a line graph.

Abbreviations and symbols: DPC = dry powder capsules; MDI = metered-dose inhaler; PL = placebo; > indicates significantly greater efficacy; ≡ indicates similar efficacy (not significantly different).

given 15 minutes before exercise. Although formoterol 12μg and salbutamol 200μg were also equally effective in preventing EIA when administered 2 hours before exercise, formoterol 12μg provided significantly better protection than salbutamol 200μg when given 4 hours before exercise.

More recent studies have extended these findings to show that a single dose of formoterol 12μg provides protection against EIA for up to 12 hours. Several double-blind, placebo-controlled studies have compared the efficacy of formoterol 12 to 24μg with that of salbutamol 200 to 400μg in patients with EIA (table V).

In all studies, the efficacy of formoterol in preventing EIA was greater than or equal to that of salbutamol when administered at 3, 8, and 12 hours before exercise. Daugbjerg et al.[68] showed that formoterol 12μg via Aerolizer® inhaler[51] resulted in a significantly smaller median percentage decrease in FEV_1 than salbutamol at both 3 and 12 hours (fig. 2). Three hours after inhalation, the median percentage decrease in FEV_1 after ≥6 minutes of treadmill exercise was 9% for formoterol compared with 17% for salbutamol. When formoterol was administered 12 hours before exercise, the median percentage fall in FEV_1 ranged from 8% to 11%.

Percentage protection against EIA (percentage reduction in FEV_1 with placebo minus percentage decrease in FEV_1 with treatment, divided by the decrease with placebo × 100), an indicator of the clinical importance of a statistically significant effect, was calculated in 2 recent studies in children.[68,69] Protection of 50% has been established as clinically important. Three hours after inhalation, formoterol conferred 76 to 77% protection compared with 46% with salbutamol 400μg and 17% with salbutamol 200μg. At 12 hours, the extent of protection was 70% with formoterol 12μg and 13% with salbutamol 400μg.[68] All differences between the 2 drugs were statistically significant. Similar results were obtained whether the drugs were inhaled as dry powder capsules[68,71] or aerosol.[67,69,70]

3.3 Delivery Devices

It is known that delivery devices have different deposition characteristics.[72] Formoterol has traditionally been delivered via a propellant-driven pressurised MDI. With optimal inhalation technique, these devices deliver only about 10 to 15% of the metered dose to the airways, whereas dry powder inhalers such as Turbuhaler® and Aerolizer® deliver 20 to 35% of the metered dose.[51,72] Dry powder inhalers eliminate most of the problems associated with difficulty in coordinating actuation of an MDI with inhalation. However, total drug dose delivered with dry powder inhalers appears to be sensitive to patient inspiratory flow rate.[51,73]

The therapeutic efficacy of other delivery systems for formoterol has also been studied.[61,62,72,74-76] In a multicentre, randomised, double-blind, parallel group study, involving 194 patients with mild to moderate asthma, formoterol 6, 12 and 24μg twice daily via Turbuhaler® was more effective than placebo in improving morning (increase of 40 *vs* 9 L/min) and evening (increase of 35 *vs* 3 L/min) PEF, reducing asthma symptoms and decreasing rescue medication requirements.[74] In this study, the lowest dose to control clinical symptoms effectively and improve lung function, as measured by morning and evening PEF, was 6μg twice daily (fig. 3). The efficacy of formoterol 6μg twice daily via Turbuhaler® has been confirmed in a comparison with terbutaline administered by the same device (section 3.1.3). Studies that assessed the efficacy of formoterol administered via Turbuhaler® when added to existing inhaled corticosteroid regimens are discussed in section 3.1.4.

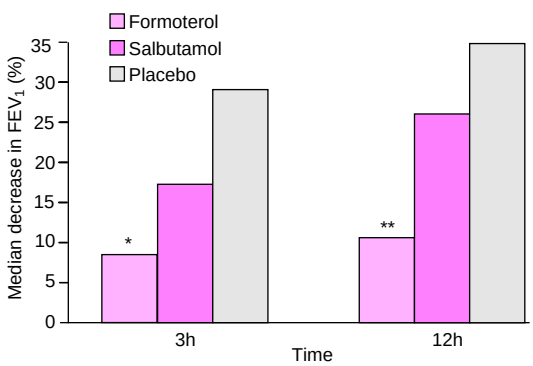

Fig. 2. Median percentage decrease in forced expiratory volume in 1 second (FEV_1) in 16 asthmatic children after exercise at 3 and 12 hours after administration of placebo, formoterol 12μg via Aerolizer® inhaler[51] or inhaled salbutamol 400 μg.[68] *Symbols:* * $p < 0.05$, ** $p < 0.01$ *vs* salbutamol.

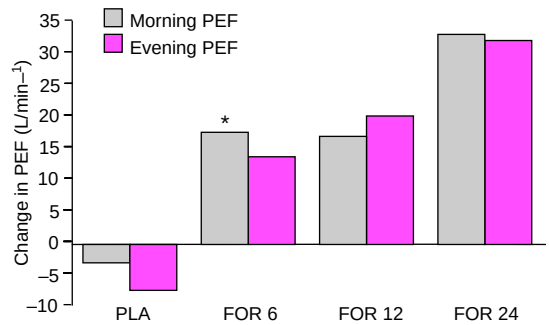

Fig. 3. Effect of treatment with formoterol 6, 12 or 24μg twice daily via Turbuhaler®, or placebo, on PEF in 194 patients with moderate asthma.[74] *Abbreviations and symbol:* FOR 6 = formoterol 6μg; FOR 12 = formoterol 12μg; FOR 24 = formoterol 24μg; PEF = peak expiratory flow, PLA = placebo; * $p < 0.008$ *vs* placebo.

Another new multiple-dose, dry powder inhalation device has been tested recently in 18 patients.[4] Patients received placebo or formoterol 6, 12 or 24μg twice daily for 4 treatment periods of 8 days each. All doses of formoterol elicited significant increases in FEV_1 between 1 and 12 hours in comparison with placebo. The effectiveness of formoterol 24μg (as measured by FEV_1) was significantly superior to that of formoterol 12 and 6μg. The efficacy of formoterol 6μg with this device seemed to wane at 8 hours, and the efficacy of all doses decreased between 12 and 24 hours after inhalation.

4. Tolerability

All formulations of formoterol are well tolerated.[1] Oral formoterol and high doses of inhaled formoterol are associated with a greater incidence of adverse events than are the recommended inhaled doses 6 to 24μg. Adverse events commonly

reported with inhaled formoterol are those traditionally associated with the use of β_2-agonists. In general, the most common adverse events reported are tremor, palpitation, headache and muscle cramps.[1,53,56] In adults, the incidence of adverse events with inhaled formoterol has ranged from 0% to 11% in large, long term studies of 9 to 20 months duration.[44,46] Clinically insignificant electrocardiogram (ECG) changes were reported in 3 of 116 (2.6%) patients treated with inhaled formoterol 12μg twice daily;[46] a clinically significant ECG abnormality that was possibly related to treatment with formoterol 12μg twice daily has been reported in only 1 patient.[45] In clinical studies, significant cardiovascular effects have not been reported in patients treated with therapeutic doses of formoterol. Changes in heart rate and blood pressure have been minimal, probably as a result of the marked β_2-selectivity of formoterol and have not been considered clinically significant.[1]

In comparative trials with terbutaline and salbutamol, formoterol was as well tolerated as the comparator drug.[54,58,61] Tremor was reported in 6% of patients treated with formoterol versus 2% of patients treated with salbutamol, but the difference was not significant.[58] Tolerability in elderly patients (n = 198; mean age 71 years) has been studied in a recent trial comparing formoterol and salbutamol. Both drugs were equally well tolerated. No significant changes in laboratory values, heart rate, blood pressure, or ECG tracings were noted.[52]

Adverse events occurred in 26% of 82 asthmatic children who received formoterol 12 and 24μg inhaled as dry powder capsules twice daily for 1 year. Most of the adverse events related to the respiratory tract.[49] Children tolerated the syrup formulation well, although 1 child had a single episode of severe tremor that was alleviated by terminating treatment.[1]

In a single-dose study comparing the tolerability of formoterol 12, 24 and 48μg dry powder capsules with that of formoterol 12μg via a MDI, and placebo, Maesen et al.[2] reported that there were no significant differences in heart rate when formoterol 12μg was administered via either device. Formoterol 48μg significantly increased heart rate compared with all other doses, although the increase (3 beats per minute) was not clinically significant. In another single-dose study,[77] tremor response to formoterol 12 and 24μg was compared when both doses were inhaled as either solution or suspension aerosol. The higher dose of each formulation produced increased tremor amplitude compared with the lower dose and the tremor response to suspension aerosol was higher than that to solution aerosol. These results[2,77] support a dose-dependent effect on adverse events, although not all studies have confirmed this effect.[46]

5. Dosage and Administration

The current recommended dosage of inhaled formoterol for adults and children 6 years and older is 6μg twice daily via Turbuhaler®, or 12μg (1 puff) twice daily via Aerolizer® or other dry powder devices, or MDI. If the recommended dosage does not sufficiently control symptoms, it may be increased to 24μg twice daily and subsequently be titrated according to effect. Dosage should be individualised.

In Europe, dose may be expressed as that delivered to the patient, 4.5 to 18μg, rather than the metered dose of 6 to 24μg.

The recommended dosage of oral formoterol is 80μg 2 or 3 times daily in adults and 1.5 μg/kg 2 or 3 times daily in children. Dry syrup, at a dosage of 4 μg/kg/day in 2 to 3 divided doses, is recommended for children.[1] Dosage recommendations for parenteral formoterol are not available.

Formoterol should be administered in conjunction with regular doses of inhaled or oral corticosteroids.[78-81] The current recommendations for the use of formoterol are as an alternative to increased dosages of inhaled corticosteroids in patients who remain symptomatic while receiving low to moderate doses of inhaled corticosteroids.[82,83]

Formoterol is a long-acting β_2-agonist currently recommended for maintenance therapy and should not be used to treat acute exacerbations of asthma. For a full list of contraindications, see the previous

review in *Drugs*.[1] Patients should be warned not to discontinue therapy with corticosteroids while on formoterol, although adjustment of corticosteroid dosage may be possible. As with any bronchodilator, reduced efficacy of formoterol may indicate a worsening of asthma.

6. Place of Formoterol in the Management of Asthma

Since the recognition of the importance of inflammation in asthma, guidelines[81-86] have recommended the regular use of anti-inflammatory drugs as first-line maintenance therapy in patients in whom asthma symptoms are not controlled by occasional use of short-acting β_2-agonists. Because of a possible link between asthma death and high doses of short-acting β_2-agonists, current guidelines recommend that short-acting β_2-agonists should be used only intermittently for symptom relief.

Since the last review in *Drugs*, the role of an inhaled long-acting selective β_2-agonist in the management of asthma has been further clarified. The principles of pharmacological management of chronic asthma as stipulated in the UK and US guidelines are based on an approach comprising 4 or 5 steps. Patients start treatment at the step most appropriate to the initial severity of their asthma. The number of drugs and dosage are increased as the disease becomes more severe. Based on the assessment of new scientific evidence it is recommended that long-acting β_2-agonists be used an alternative to increasing the dosage of inhaled corticosteroids in patients whose asthma symptoms are poorly controlled with a regular regimen of low to moderate doses of inhaled corticosteroids and short-acting β_2-agonists as needed.[82,83] Although *in vitro* studies suggest that formoterol may have some anti-inflammatory properties, clinically relevant effects on chronic airway inflammation have not been demonstrated; therefore, formoterol should be used in conjunction with an anti-inflammatory agent.

Formoterol, a selective β_2-agonist, produces effective and prolonged bronchodilation in patients with asthma. In clinical studies, the efficacy and tolerability of formoterol have compared favourably with those of shorter-acting β_2-agonists such as salbutamol, terbutaline and fenoterol. Furthermore, patients have preferred formoterol over alternative bronchodilators. In addition, formoterol has been more effective than comparators in preventing EIA and in the prophylaxis of nocturnal asthma. In single-dose studies, the onset of action of formoterol has been more rapid than that of salmeterol, another long-acting selective β_2-agonist, and roughly equal to that of salbutamol. The duration of action has been similar for formoterol and salmeterol.

Earlier guidelines for the management of chronic asthma in adults recommended increasing inhaled steroid dosage before adding a long-acting β_2-agonist. However, new guidelines from the UK[82] and US[83] suggest adding a long-acting β_2-agonist as an alternative option to increasing steroid dosage in patients with persistent asthma symptoms despite treatment with low to moderate doses of inhaled corticosteroids, especially in patients with nocturnal asthma symptoms or sensitivity to exercise. Results of a double-blind study which investigated the efficacy of adding formoterol 12μg twice daily via Turbuhaler® to low (200 μg/day) and moderate dose (800 μg/day) budesonide indicated that the addition of the long-acting β_2-agonist significantly reduced the frequency of severe asthma exacerbations compared with placebo.[63] Preliminary results also indicate that adding formoterol to inhaled beclomethasone dipropionate 500μg daily improved lung function, more than doubling the dosage of the inhaled steroid.[65] Similarly, studies with salmeterol have shown that the addition of the long-acting β_2-agonist to low (400 μg/day)[87] or moderate (1000 μg/day)[88] dosages of beclomethasone dipropionate improved lung function and controlled symptoms better than increasing the dosage of inhaled steroids. These results support the therapeutic guidelines that recommend adding a long-acting β_2-agonist to low doses of inhaled corticosteroids in patients with persistent symptoms or less than optimal lung function. Formoterol may be especially helpful in

persistent symptoms or less than optimal lung function. Formoterol may be especially helpful in patients with nocturnal asthma or EIA. It has been suggested that combined therapy with inhaled steroids and a long-acting β_2-agonist may be more effective than steroids alone because of the complementary action of the two drugs.[89]

The precise role of formoterol in the management of acute asthma remains to be clarified. Although its onset of action is similar to salbutamol, formoterol is not recommended for use as rescue medication in acute asthma. Because of its long duration of action, formoterol may mask signs that more aggressive therapy is warranted. However, the use of formoterol in the acute setting has not been evaluated.

In conclusion, formoterol twice daily is generally more effective than and as well tolerated as shorter-acting β_2-agonists in treating patients with asthma. In single-dose studies, formoterol and salmeterol have similar bronchodilatory effects and are equally prolonged in their action, but formoterol has a more rapid onset of action than salmeterol. Clinical studies comparing the two long-acting agents in the long term treatment of asthma have yet to be published.

Formoterol is currently recommended for use in symptomatic patients taking low to moderate doses of inhaled steroids as an alternative to increasing corticosteroid dosage. Further appropriately designed studies comparing these two alternative treatment regimens and analyses to define features predictive of individual patient responses are needed. Patients with mild to moderate asthma who have EIA or nocturnal asthma symptoms may particularly benefit from the long duration of action of formoterol. Studies of longer duration and evaluating the earlier use of formoterol in patients with mild to moderate asthma will further clarify its safety and optimum role in the management of asthma.

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