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The 24 h duration of bronchodilator action of the salmeterol/fluticasone combination inhaler

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Asthma;
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Summary *Introduction*: The duration of bronchodilator action of the long-acting beta agonist salmeterol when administered in the evening has not been investigated. In this study we have investigated whether a single evening dose of salmeterol, administered from the combination salmeterol/fluticasone (SFC) Accuhaler significantly attenuates the circadian rhythm in airway tone over 24 h.

Methods: Eighteen subjects with mild to moderate asthma (mean FEV_1 84% predicted) participated in a double-blind, double dummy, placebo controlled, cross-over study. Subjects inhaled, in random order, placebo, salbutamol (200 μg) or SFC (50/100 μg) administered in the evening (2000 h) on three separate occasions. Lung function measurements including FEV_1, specific airways conductance (sGaw) and maximum expiratory flow at 25–75% of vital capacity ($MEF_{25-75\%}$) were assessed at baseline, at 1 h and subsequently every 4 h post-dose for 24 h.

Results: Compared with placebo, SFC significantly improved the three measures of airways function throughout the 24 h period, with a difference in FEV_1 at 24 h of 0.24 l (0.00–0.47 l). SFC abolished the biphasic pattern of the circadian rhythm in airway tone. In contrast, salbutamol had a significant bronchodilator action of 4–8 h, depending on the lung function parameter measured.

Conclusion: The single evening administration of SFC via the Accuhaler resulted in a duration of bronchodilation of at least 24 h, with the abolition of the accentuated biphasic circadian variation in airway tone observed in asthma.

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Introduction

While the efficacy of long-acting beta agonist drugs are well established, their recommended use has changed significantly since their introduction over 10 years ago. Initially long-acting beta agonists were reserved for patients with severe asthma, however recent international guidelines now recommend their use at Step 3, in moderately severe patients not well controlled on low dose inhaled corticosteroid therapy.[1,2] The use of long-acting beta agonists with inhaled corticosteroids from combination inhaler devices ensures that long-acting beta agonist drugs are not prescribed as monotherapy and improves compliance with inhaled corticosteroids.[3]

The incorporation of once daily dosing is another important strategy to improve compliance, and is a regime preferred by most patients.[4,5] However, before considering such a once daily regime with combination long-acting beta agonist/inhaled corticosteroid therapy, it would be necessary to investigate whether its use results in adequate bronchodilation and anti-inflammatory effects. While the efficacy of inhaled corticosteroids administered once daily has been widely studied,[6] this is not the case for the long-acting beta agonists salmeterol or formoterol. To date there have been few placebo-controlled studies of the bronchodilator time course of action over a 24 h period, following administration in the morning[7–9] and only a single study following evening administration.[10] However, if long-acting beta agonists are to be used once daily, it would seem preferable that they are administered in the evening to ensure that the maximum bronchodilator effect occurs during sleep when the enhanced circadian rhythm results in the greatest degree of bronchoconstriction. In this study we have investigated whether a single dose of the combination salmeterol/fluticasone (SFC) via an Accuhaler would significantly attenuate the circadian variation in airway tone and achieve bronchodilation for at least 24 h.

Methods

Subjects

Patients volunteering for this study were recruited from newspaper advertising and from a database of asthma volunteers. All subjects had to meet the following criteria:

age 16–65 years; stable asthma; baseline forced expiratory volume in 1 s (FEV_1) $\geqslant$50% predicted; $\geqslant$15% reversibility in FEV_1 (measured 15–30 min after 400 μg of inhaled salbutamol via MDI and spacer) or a documented history of 15% reversibility after inhaled beta agonist within three months prior to the start of the study.

Exclusion criteria comprised a respiratory tract infection or asthma exacerbation within 1 month of entry into the study. Following enrolment, subjects were withdrawn if their baseline FEV_1 on one of the study days was $<$50% predicted. The study was approved by the Wellington Ethics Committee and written informed consent was obtained from all the subjects.

Study design

This was a double-blind, double-dummy, placebo-controlled cross-over study. Subjects were admitted to Bowen Hospital for 24 h on three occasions and slept overnight, being woken up for lung function measurements. There was at least a 3-day interval between study days. Those patients already taking a long-acting beta agonist abstained from using this medication for 2 weeks prior to, and for the duration of the study. During this 2 week period and between treatment days, subjects continued with the regular dose of their inhaled corticosteroid therapy, and salbutamol aerosol as required. On each of the study days patients took their normal morning dose of inhaled corticosteroid but withheld their evening dose. Smoking and drinks containing caffeine were forbidden on study days. Patients were instructed on current inhaler technique.

After the assessment of lung function (1915–2000 h), patients were instructed to inhale placebo, salbutamol (2×100 μg), or SFC ($1 \times 50/100$ μg), in random order from blinded Accuhalers (placebo and SFC) and metered-dose inhalers plus spacer (placebo and salbutamol). Patients were dosed at either 2000, 2010, 2020, 2030 or 2040 h. Patients were dosed at the same time on each study day ($\pm$10 min).

Lung function was measured at baseline, 1 h post-dose, and then subsequently every 4 h post-dose until the next evening (2100, 2400, 0400, 0800, 1200, 1600 and 2000 h). Measurements of lung function included FEV_1, airways resistance (Raw), specific conductance (sGaw) and maximum expiratory flow at 25–75% of forced vital capacity ($MEF_{25-75\%}$). FEV_1 and $MEF_{25-75\%}$ were recorded at the mouth using a pneumotacograph with electronic integration (Jaeger, Wurzburg, Germany). The highest value of three manoeuvres was retained as per ATS guidelines. sGaw was calculated from

airways resistance and thoracic gas volume, measured with a constant volume body plethysmograph (Jaeger, Wurzburg, Germany).

Data analysis

The primary outcome variable was FEV_1, with sGaw and $MEF_{25-75\%}$ representing the secondary outcome variables. Two forms of mixed linear models were used to model the cross-over with repeated measures design.[11,12] Firstly an analysis of covariance model using the baseline reading of the particular outcome as a covariate, and accounting for the repeated measures by specifying a variance–covariance matrix. A covariance structure that resulted in a smaller value of 'Akaikes information criterion' was used for each outcome variable. If the time by treatment interaction term in the analysis of covariance was significant, a set of contrasts was estimated for the difference between each of the two active treatments and placebo at 4, 8, 12, 16 and 24 h. The type 1 error rate was controlled by choosing an appropriate number of contrasts determined by the degrees of freedom for the time by treatment interaction term. Secondly a random coefficients model was formed. The best fitting model specified cubic polynomial functions for the salbutamol and placebo arms, to model the biphasic pattern of airflow, and a linear function for the salmeterol and fluticasone arm. SAS version 8.2 was used.

Results

Eighteen mild to moderate asthmatics with a mean (range) age of 40 (18–60) years and a mean (range) FEV_1 of 84% (58–110%) predicted were investigated (Table 1). The mean pre-trial inhaled corticosteroid dose was 717 μg/day (range 0–2000 μg/day) of beclomethasone dipropionate (BDP) or equivalent. One subject was an infrequent smoker of approximately two pack years who abstained for the duration of the study. One subject who was withdrawn from the study at Visit 1 as her baseline FEV_1 was $<50\%$ was replaced by another subject. No subjects required rescue medication on any of the study days.

The baseline values for FEV_1, sGaw and MEF_{25-75} were not significantly different on the three study days ($P>0.05$). The mean (SD) for FEV_1 was 2.62 (0.90) l before inhalation of placebo, 2.52 (0.90) l before inhalation of salbutamol and 2.67 (0.92) l before inhalation of SFC.

Table 1 Patient characteristics.

Subject no.	Sex	Age (years)	Baseline ICS μg/day (BDP or equiv)	FEV_1 (% pred)
1	F	27	800	93
2	F	60	400	87
3	M	20	1000	110
4	F	46	1000	69
5	F	59	200	84
6	F	57	1000	83
7	F	56	500	81
8	M	18	200	92
9	F	47	400	70
10	M	60	1500	78
11	M	24	1000	80
12	F	21	0	80
13	F	30	400	92
14	F	44	200	90
15	F	26	500	90
16	F	51	2000	58
17	M	50	800	100
18	F	22	1000	73
Mean	—	40	717	84
Range	—	18–60	0–2000	58–110

Following the administration of placebo there was a typical biphasic change in airway tone over 24 h with a nadir around 0400 h (8 h post dose) and a peak at around 1200 h (16 h post dose) (Figs. 1–3). The administration of SFC resulted in significant bronchodilation throughout the 24 h period when compared with placebo. This significantly greater magnitude of bronchodilation was observed with all three measures of lung function (Tables 2 and 3), with a difference in FEV_1 at 24 h of 0.24 l (95% CI 0.00–0.47 l). Following the administration of SFC there was a gradual linear decline in lung function throughout the 24 h period which contrasted with the biphasic pattern observed with both placebo and salbutamol (Figs. 1–3). Salbutamol had a significant bronchodilator action of up to 4–8 h, depending on the lung function parameter measured (Tables 2 and 3). The initial phase of the biphasic pattern of lung function was higher following salbutamol than placebo, however the measurements were similar after the nadir at 0400 h (8 h post dose).

The figures show the estimated polynomial plots together with the raw values for the outcome variables. Table 4 shows the actual estimated coefficients and their standard errors for the FEV_1 measurement. Additional polynomial terms to the SFC and removal of higher order terms for the other treatments were not statistically significant and did not improve the fit of the model.

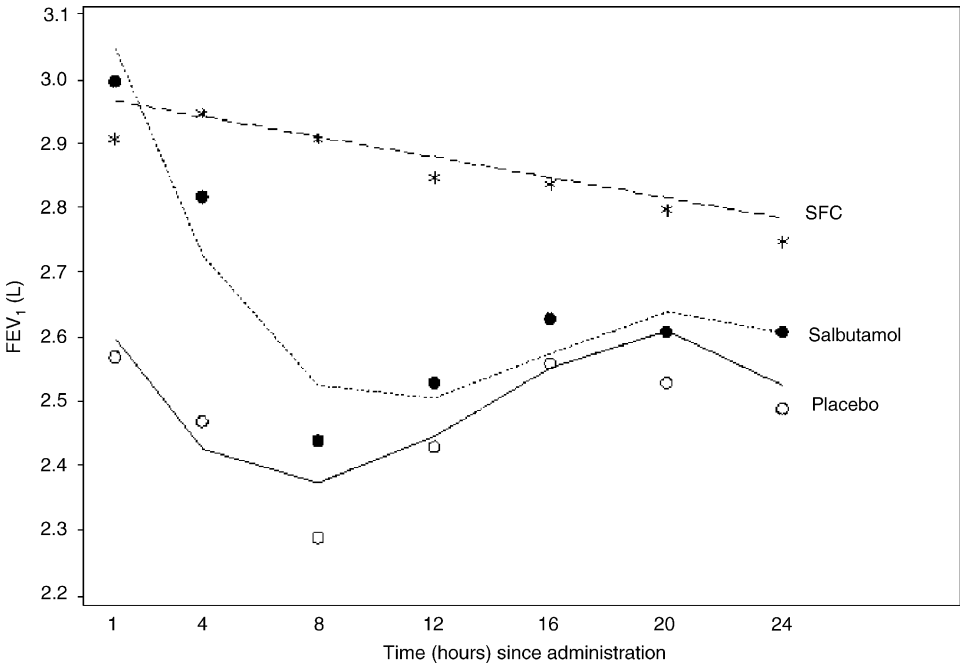

Figure 1 Plot of raw mean FEV_1 values for each treatment arm: placebo (○), salbutamol (●), SFC (∗), and fitted polynomial functions, placebo (——), salbutamol (·····), SFC (– – –).

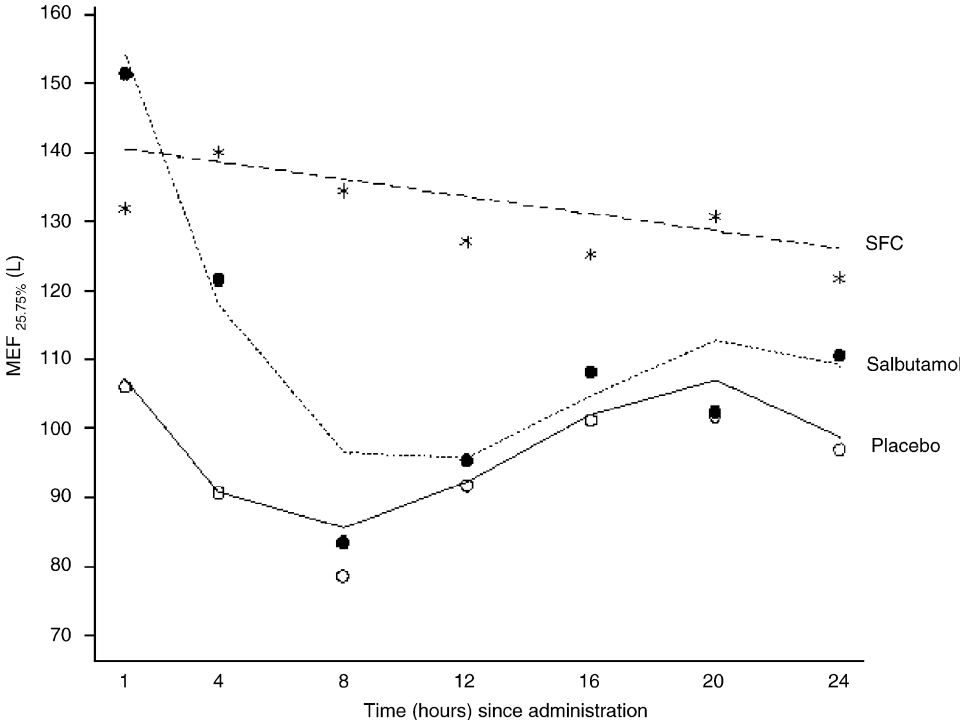

Figure 2 Plot of raw mean MEF values for each treatment arm: placebo (○), salbutamol (●), SFC (∗), and fitted polynomial functions, placebo (——), salbutamol (·····), SFC (– – –).

Discussion

This study has shown that the evening administration of SFC (50/100 μg via Accuhaler) results in bronchodilation which persists for at least 24 h. The biphasic pattern of airway function which was observed in the placebo and salbutamol groups was abolished with the administration of SFC.

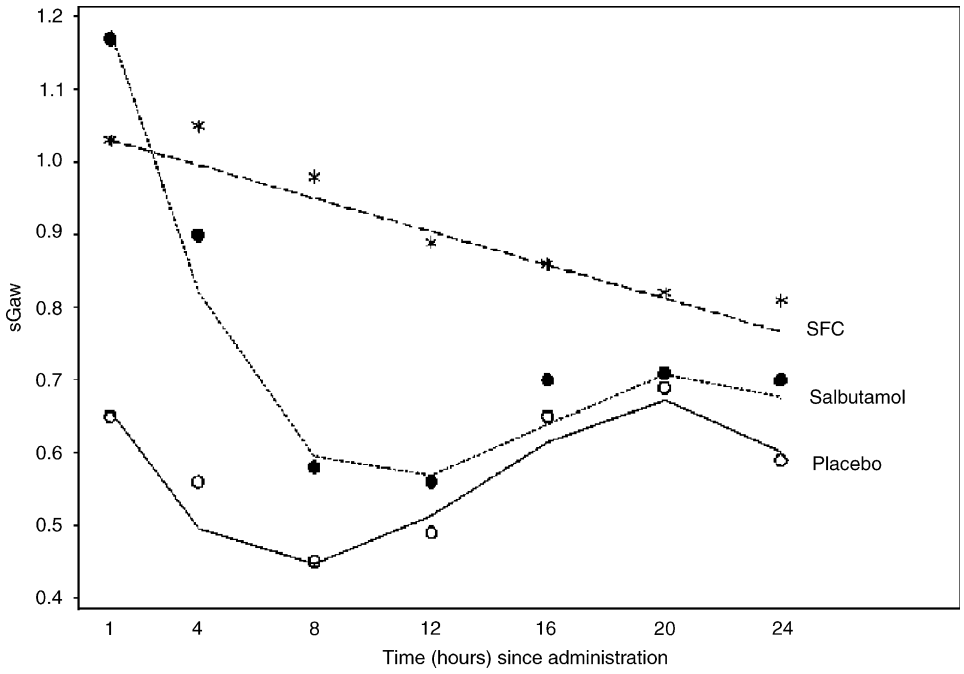

Figure 3 Plot of raw mean sGaw values for each treatment arm: placebo (○), salbutamol (●), SFC (∗), and fitted polynomial functions, placebo (——), salbutamol (·····), SFC (– – –).

Table 2 Airway tone over 24 h.

Time	Placebo		Salbutamol		SFC	
	FEV_1	sGaw	FEV_1	SGaw	FEV_1	sGaw
Baseline	2.62 (0.9)	0.72 (0.25)	2.52 (0.9)	0.73 (0.32)	2.67 (0.92)	0.74 (0.32)
1 h	2.6 (0.9)	0.65 (0.36)	3.0 (1.0)	1.17 (0.30)	2.9 (1.0)	1.03 (0.36)
4 h	2.5 (0.8)	0.56 (0.15)	2.8 (1.0)	0.90 (0.24)	3.0 (1.1)	1.05 (0.34)
8 h	2.3 (0.7)	0.45 (0.12)	2.4 (0.7)	0.58 (0.14)	2.9 (1.1)	0.98 (0.29)
12 h	2.4 (0.8)	0.49 (0.16)	2.5 (0.8)	0.56 (0.15)	2.8 (1.0)	0.89 (0.36)
16 h	2.6 (0.9)	0.65 (0.19)	2.6 (0.9)	0.70 (0.21)	2.8 (1.0)	0.86 (0.26)
20 h	2.5 (0.9)	0.69 (0.26)	2.6 (0.9)	0.71 (0.22)	2.8 (1.0)	0.82 (0.24)
24 h	2.5 (0.9)	0.59 (0.20)	2.6 (0.9)	0.70 (0.19)	2.8 (1.0)	0.81 (0.26)

FEV_1=forced expiratory volume in 1 s.
sGaw=specific airways conductance.
Mean (standard deviation).

A number of methodological issues were considered in the design of this study relevant to the interpretation of the findings. The first was the use of both placebo and salbutamol arms in the cross-over design. Placebo was used due to the marked circadian variation in airway calibre that occurs in asthma as a result of cyclical variations in the inflammatory processes within the airway wall combined with the circadian variation of vagal activity and endogenous cortisol production.[13–16] This was illustrated in our study in which patients with apparently clinically stable asthma exhibited considerable circadian variation in airway tone despite regular treatment with inhaled corticosteroids, with a greater than 10% fall in FEV_1 at the nadir at 0400 h. The lack of a placebo arm to determine the baseline circadian rhythm in lung function has severely limited the interpretation of some previous time course studies of long-acting beta agonist drugs.[17,18] The salbutamol arm was included as a "control" bronchodilator treatment, thereby ensuring that both the patient and the investigators remained blinded to the active medication.

Another issue was the use of different measures of lung function to reflect different sites of the

Table 3 SFC, salbutamol and placebo cross-over trial—differences between active arms and placebo at specified time points.

Time after administration	Treatment comparison	FEV_1		sGaw		MEF	
		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
4 h	SFC minus placebo	0.46 (0.23–0.69)	0.0002	0.49 (0.34–0.64)	<0.0001	47.9 (24.2–71.5)	0.0001
	Salbutamol minus placebo	0.47 (0.23–0.70)	0.0001	0.33 (0.19–0.48)	<0.0001	35.4 (11.9–59.0)	0.004
8 h	SFC minus placebo	0.59 (0.36–0.82)	<0.0001	0.53 (0.38–0.67)	<0.0001	54.3 (30.6–77.9)	<0.0001
	Salbutamol minus placebo	0.26 (0.03–0.49)	0.03	0.12 (−0.02 to 0.27)	0.09	9.3 (−14.3 to 32.8)	0.43
12 h	SFC minus placebo	0.39 (0.16–0.62)	0.001	0.39 (0.24–0.54)	<0.0001	33.9 (10.2–57.5)	0.006
	Salbutamol minus placebo	0.21 (−0.02 to 0.44)	0.07	0.06 (–0.09 to 0.21)	0.42	8.3 (−15.3 to 31.8)	0.49
16 h	SFC minus placebo	0.25 (0.02–0.48)	0.03	0.21 (0.06–0.36)	0.005	22.7 (−1.0 to 46.3)	0.06
	Salbutamol minus placebo	0.19 (−0.05 to 0.42)	0.11	0.05 (−0.09 to 0.20)	0.49	11.6 (−12 to 35.1)	0.33
20 h	SFC minus placebo	0.23 (−0.01 to 0.46)	0.06	0.13 (−0.02 to 0.27)	0.09	23.6 (−0.1 to 47.3)	0.05
	Salbutamol minus placebo	0.18 (−0.1 to 0.41)	0.13	0.02 (−0.13 to 0.17)	0.80	5.2 (−18.4 to 28.7)	0.66
24 h	SFC minus placebo	0.24 (0.0–0.47)	0.04	0.21 (0.06–0.36)	0.005	22.3 (−1.4 to 46.0)	0.07
	Salbutamol minus placebo	0.23 (0.0–0.46)	0.05	0.10 (−0.05 to 0.25)	0.17	15.4 (−8.3 to 39.0)	0.20

bronchodilator effect. Measurement of sGaw was undertaken as this is a sensitive measure of large airway function which is measured in the tidal breathing range.[19] Together with the measurement of $MEF_{25-75\%}$ which was used to assess small airway function, SGaw has the advantage of being effort independent.[19,20] The primary outcome variable FEV_1 was measured to obtain an integrated assessment of both small and large airway function.[20] A similar bronchodilator duration of action was observed following SFC with all three methods used to assess airway calibre, suggesting that the bronchodilator efficacy was present throughout airways of varying size. The FEV_1 also provided a measure of lung function with which physicians are clinically familiar. In this regard, we propose that the magnitude of the 0.24 l improvement in FEV_1 24 h after administration of SFC compared with placebo is of clinical significance.

The decision to administer salmeterol from a combination rather than a separate inhaler was made due to the clinical preference for prescribing long-acting beta agonist therapy in combination with inhaled corticosteroids. This combination regime ensures that salmeterol is not prescribed as monotherapy and encourages compliance with inhaled corticosteroids through its co-administration.[3] However, administration of inhaled corticosteroids has been shown to result in a small acute bronchodilator effect[21,22] and it is therefore possible that a minor proportion of the bronchodilator effect we observed with SFC in this study may have resulted from the fluticasone component. In addition, there is evidence that inhaled corticosteroids may enhance the bronchodilator effects of long-acting beta agonists when given concurrently,[23] particularly when administered from a combination inhaler rather than with separate inhaler therapy.[24] As a result, our results relate to salmeterol when co-administered with fluticasone from a combination inhaler, and we are unable to determine the duration of bronchodilator activity of salmeterol alone when given in the evening. Likewise, we were unable to determine whether fluticasone had any bronchodilator activity when given alone in the evening.

A salmeterol dose of 50 μg administered via an Accuhaler was chosen as dose–response studies have demonstrated that this can be considered to be the optimal dose in terms of both efficacy and side effects.[7,8,18,25] The evening administration of SFC was chosen because it seemed logical to administer salmeterol prior to sleep, when the enhanced circadian rhythm in asthma results in the greatest degree of bronchoconstriction with the associated risk of morbidity and mortality.[26,27]

Table 4 FEV_1—estimated coefficients for polynomial model.

Treatment	Parameter	Estimate (standard error)	*P*
Placebo	Intercept	2.7 (0.22)	<0.0001
	Time	−0.10 (0.02)	<0.0001
	$Time^2$	0.009 (0.002)	<0.0001
	$Time^3$	−0.0002 (0.00005)	<0.0001
Salbutamol	Intercept	3.2 (0.22)	<0.0001
	Time	−0.16 (0.02)	<0.0001
	$Time^2$	0.01 (0.002)	<0.0001
	$Time^3$	−0.0002 (0.00005)	<0.0001
SFC	Intercept	3.0 (0.22)	<0.0001
	Time	−0.008 (0.002)	<0.001

Although it has yet to be determined whether inhaled corticosteroids may have a greater effect when given in the evening compared with the morning, such an evening regime would seem preferable for similar reasons in that the greatest magnitude of airways inflammation is observed overnight.[28] The standard 100 μg dose of fluticasone administered in the SFC combination was based on the recent evidence that 80–90% of the maximum obtainable benefit with fluticasone is achieved with 100 μg of fluticasone twice daily.[29]

Our findings differed to some degree from those of the landmark study by Rabe et al.[7] which demonstrated that the bronchodilator effect of salmeterol on FEV_1 was not significantly different from placebo beyond 12 h when administered in the morning. Furthermore, in that study neither the phase nor the amplitude of circadian variation over 24 h was different between salmeterol and placebo. In children, a 50 μg dose of salmeterol via a MDI with spacer in the morning resulted in significant bronchodilation at 12 h but not 24 h, although the lack of airway measurements between these time points prevented accurate determination of the duration of bronchodilation.[9]

Following the administration of salmeterol at 1800 h, Fitzpatrick et al. reported that the nocturnal pattern of airway tone was not affected despite significant bronchodilation, although the lack of standardisation of the night-time peak flow recordings limits interpretation of this observation.[21] In contrast, Bootsma et al. reported that significant bronchodilation occurred at 20 (but not 34) h after a 50 μg dose of salmeterol delivered by MDI at 2200 h.[10] The magnitude of the difference in FEV_1 at 20 h with salmeterol compared with placebo was 10.4% of predicted values, similar to that observed in our study. No correlation was found between the bronchodilation and protection against provoked bronchoconstriction provided by salmeterol at any time point in this study, indicating that the protection of salmeterol is not predominantly caused by its bronchodilator activity. In the study by Kemp et al.,[8] both the 50 and 100 μg doses of salmeterol administered in the morning resulted in significant bronchodilation at 24 h, although the lack of circadian variation in lung function following placebo and the >15% bronchodilator response to placebo limits the interpretation of this study. Taken together these findings would suggest that a long-acting beta agonist may have a greater duration of bronchodilator action and provides better protection against nocturnal bronchoconstriction when administered in the evening compared with morning dosing. However, this issue has yet to be examined and will need to be investigated in specific clinical trials.

In summary, the results of this study show that administration of the combination SFC (50/100 μg) Accuhaler in the evening provides significant improvement in lung function over 24 h.

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