Systemic and bronchodilator effects of inhaled rac-formoterol in subjects with chronic obstructive pulmonary disease: a dose–response study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The long-acting inhaled β_2 -agonist formoterol has systemic effects when taken in high doses.
- It can be used as relief medication in asthma and there is interest in this approach in chronic obstructive pulmonary disease (COPD).
- Relief medication can involve high doses, and in subjects with COPD who have limited ability to bronchodilate the adverse effects can outweigh the benefits.
- There are concerns with the overall safety of high-dose β_2 -agonists in subjects with COPD, and this study looks at the balance of beneficial and adverse effects of a range of doses of inhaled formoterol.

WHAT THIS STUDY ADDS

- Among subjects with COPD, high-dose inhaled formoterol produced a dose-related increase in forced expiratory volume in 1 s without a corresponding reduction in dyspnoea or increase in walk distance.
- Systemic effects were modest, however, and high doses did not appear to reduce patient satisfaction.
- Although further safety data are needed, inhaled formoterol may have a role as relief medication in COPD.

AIMS

Rac-formoterol is effective as maintenance treatment for both asthma and chronic obstructive pulmonary disease (COPD) and is now used as relief therapy in asthma. Using rac-formoterol for relief and maintenance treatment could involve inhalation of high doses, and whether this is of benefit in COPD is uncertain. Our aim was to determine whether higher doses of inhaled rac-formoterol produce systemic adverse effects that outweigh the limited bronchodilator benefit seen in subjects with COPD.

METHODS

We examined airway and systemic effects of 6, 12, 24 and 48 μ g rac-formoterol and placebo on separate days in 20 subjects with symptomatic COPD [forced expiratory volume in 1 s (FEV₁) 47% predicted]. FEV₁, oxygen saturation, dyspnoea, 6-min walk distance, patient satisfaction and systemic effects were measured and treatment was assessed against placebo and for dose–response effects.

RESULTS

FEV₁ [area under the time–response curve (AUC)] and satisfaction scores increased with all formoterol doses compared with placebo, as did AUC tremor with the 24- and 48- μ g doses and AUC heart rate with the 48- μ g dose. A dose–response relationship was seen with FEV₁ and tremor, but not with satisfaction scores. There was no difference between placebo and rac-formoterol for other variables.

CONCLUSIONS

Our results show that in patients with COPD rac-formoterol improves FEV₁ and patient satisfaction without a corresponding reduction in dyspnoea. Since the systemic effects from a relatively high dose were minimal, its use as relief medication in COPD merits further evaluation.

Introduction

Bronchodilators are widely used by patients with symptomatic chronic obstructive pulmonary disease (COPD). Short-acting agents are used for symptom relief, but long-acting β_2 -agonists have additional benefits [1, 2], and management algorithms recommend their introduction if symptoms persist [3].

Rac-formoterol, a selective β_2 -agonist with a 12-h duration of action at conventional doses, has been shown to improve lung function and reduce symptoms when inhaled twice daily by patients with COPD [1, 4]. Its rapid onset of action within 5 min [5, 6] has led to it being used as relief medication in asthma, and this approach was more effective than rac-terbutaline in terms of improving lung function and prolonging the time to the first severe exacerbation [7].

A similar strategy has been suggested for patients with COPD [8], but the balance of beneficial and adverse effects may be different since additional bronchodilation with higher doses may be minimal in these patients, whereas the potential for adverse effects will increase. The main safety concern with high-dose rac-formoterol relates to cardiovascular adverse effects. This is an important consideration among patients with COPD, who may have coexisting ischaemic heart disease and hypoxaemia, both risk factors for cardiac arrhythmia.

We therefore carried out a randomized, crossover dose-response study to compare efficacy, systemic effects and subject satisfaction following single doses of inhaled rac-formoterol (6, 12, 24 and 48 μ g) and placebo in 20 patients with symptomatic COPD.

Methods

Subjects

Patients aged 40–85 years with a clinical diagnosis of COPD were recruited if they had exertional breathlessness, limited reversibility to inhaled salbutamol 200 μ g (<200 ml), a forced expiratory volume in 1 s (FEV₁) <70% predicted and a FEV₁/forced vital capacity (FVC) ratio of <70%. Subjects were excluded if they were current smokers [9] or had an exhaled carbon monoxide level above 10 parts per million on study days (Smokerlyser; Bedford Scientific, Rochester, UK), had experienced an acute exacerbation of COPD within 4 weeks or a myocardial infarction or unstable angina within 3 months, had an unstable medical condition or were taking β -adrenergic antagonists. Nottingham City Hospital Research Ethics Committee approved the study and written informed consent was obtained from each subject at least 24 h before the first study day.

Measurements

Oxygen saturation was measured using a fingertip pulse oximeter (Minolta Pulsox-7, Tokyo, Japan), continuous

heart rate by three-lead ambulatory monitor (DMS 300-7; Numed Cardiac Diagnostics, Sheffield, UK) and blood pressure by electronic sphygmomanometry (HEM-705CP; Omron, Tokyo, Japan). Dyspnoea and tremor were measured using a 100-mm visual analogue scale (VAS) ranging from 'no breathlessness/tremor' to 'worst possible breathlessness/tremor'. Tremor amplitude was also measured for 1 min using an accelerometer fitted to the terminal phalanx of the right middle finger with the forearm supported and the hand outstretched. The waveform was amplified and filtered to remove frequencies above 50 Hz and acceleration measured on 5-s samples using Fourier analysis (Pulse Platform; Bruel and Kjaer, Naerum, Denmark). Spirometry was performed with the patient seated using a dry bellows spirometer (Vitalograph, Buckingham, UK), taking the better of two successive measurements of FEV₁ within 100 ml. Plasma potassium concentration was measured by flame photometry (Olympus AU5000, Eastleigh, UK). A 6-min walk test was performed according to American Thoracic Society guidelines with standardized verbal encouragement [10] and with breathlessness measured on a Borg scale before and after exercise. Subjects carried out two familiarization walk tests before treatment randomization [11]. Overall satisfaction with each drug/dose was measured on a 200-mm VAS from 'completely dissatisfied, side-effects outweigh any benefit' to 'completely satisfied, benefit outweighs any side-effects'.

Study design and methods

This was a randomized, double-blind, crossover study performed on 5 days within a 2-week period and with each visit commencing at the same time of day. Subjects were required to withhold short-acting bronchodilators for at least 10 h and theophylline, tiotropium bromide and long-acting β_2 -agonists for at least 24 h before each study day. Inhaled corticosteroids and nonpulmonary medications were taken as usual unless they were known to affect any of the study outcomes. After an early breakfast with a maximum of one cup of tea or coffee, subjects attended the laboratory at 08.00 h and rested in a comfortable chair for 20 min. After checking exhaled carbon monoxide levels, the ambulatory cardiac monitor was attached and baseline measures of S_pO₂, heart rate, blood pressure, breathlessness, tremor (VAS and accelerometer) and FEV₁ were taken. Blood was then taken for plasma potassium measurement and followed by a 6-min walk test. After a further 10-min rest, subjects inhaled rac-formoterol (6, 12, 24 or 48 μ g) or placebo, with the dose and order determined by computer-generated randomized sequence. On each day and under independent supervision, subjects took four inhalations at 1-min intervals from one or more of three identical Turbhalers® containing placebo, rac-formoterol 6 μ g or 12 μ g; each device was withdrawn between inhalations to ensure blinding. Subjects remained seated for the next 4 h with repeat measures of

Table 1

Baseline characteristics for the 20 subjects

	Age, years	Sex	BMI	Pack years	FEV ₁ (l)	FEV ₁ (% pred)	FEV ₁ /FVC	Reversibility (ml) (<200 ml)	Regular β_2 -agonists
1	72	M	37	42	0.75	25	44	50	F, Sb
2	75	F	35	60	1.05	58	62	0	Sb
3	54	F	28	26	1.4	51	54	160	Sm, Sb
4	59	M	26	60	1.64	48	52	60	Sm, Sb
5	75	F	23	41	0.88	49	53	150	Sb
6	67	M	20	10	0.5	18	28	20	Sb
7	71	M	21	69	0.74	30	44	60	Sb
8	62	F	20	40	1.22	53	53	0	F, Sb
9	77	M	56	27	0.82	31	32	160	Sm, Sb
10	71	M	33	0	0.95	51	51	150	Sb
11	66	M	21	25	1.4	44	49	0	Sm, Sb
12	64	M	28	48	1.95	56	65	0	F,T
13	63	F	19	60	0.95	41	44	70	Sm, Sb
14	60	M	22	45	2.65	69	63	140	
15	62	F	34	30	1.37	59	58	100	Sm,Sb
16	60	M	21	56	0.75	23	25	50	F, Sb
17	77	M	28	0	1.4	55	50	120	Sm, T
18	75	M	22	50	1.28	42	49	80	Sm
19	52	M	29	24	2.52	68	53	0	T
20	67	M	28	75	2.11	63	54	0	Sm

F, Formoterol; Sb, Salbutamol; Sm, Salmeterol; T, Terbutaline; BMI, body mass index, FEV₁, forced expiratory volume in 1 s.

oxygen saturation, heart rate, blood pressure, breathlessness, tremor and FEV₁ in that order at 30, 60, 120, 180 and 240 min post inhalation. Every 60 min, subjects were asked, 'Have you felt any adverse effects that may relate to inhaling the medication'. At 4 h a further blood sample was taken for plasma potassium assay and the subject was asked to record overall satisfaction with the treatment. The 6-min walk test was then repeated.

We were interested in the balance between beneficial and adverse effects, but with no data available on which to base power calculations, we opted to base the calculations on FEV₁. Randomizing 20 subjects provided 80% power to detect a 160-ml change in FEV₁ [12] and allowed us to assess systemic effects of interest [13].

Analysis

The area under the curve for the variables measured at intervals over the 4 h, the change in mean plasma potassium and 6-min walk distance between baseline and 4 h and ectopic beat rate and satisfaction scores were determined for each subject and treatment. AUC was calculated by computer program and reflects the change over 4 h for each treatment. The differences between placebo and each dose of rac-formoterol were then assessed using repeated measures ANOVA and the dose–response relationship was assessed by statistical significance of the linear contrast with increasing rac-formoterol dose. All analyses were performed with SPSS Version 12 (SPSS Inc., Chicago, IL, USA), and statistical significance accepted as $P < 0.05$.

Results

All 20 subjects (six women) completed the study (Table 1). Their mean age was 66 years, mean cigarette consumption was 42 pack-years, body mass index 26 kg m⁻² and FEV₁ 1.32 l (47% predicted) with a mean increase of 33 ml (range 0–160 ml) following rac-albuterol 200 µg. Thirteen of the 20 participants used an inhaled corticosteroid and four used tiotropium bromide. Nineteen subjects used inhaled β_2 -agonists on a daily basis, with 13 taking a long-acting β_2 -agonist twice daily and six further subjects taking a short-acting β_2 -agonist four times a day.

Data were available for all time points except for three plasma potassium levels due to blood clotting. There were no significant differences in baseline FEV₁ values between study days and no crossover effects.

Response to rac-formoterol (Table 2)

FEV₁ (Figures 1 and 2) FEV₁ increased from baseline with all doses of rac-formoterol and the effect was sustained over 4 h. AUC FEV₁ was significantly higher after all doses of rac-formoterol compared with placebo and showed a significant dose–response relationship with increasing doses of rac-formoterol. The largest AUC FEV₁ (626.6 ml h⁻¹) was seen with the highest dose of rac-formoterol and reflects a mean increase in FEV₁ of around 157 ml across the 4-h time period. There was no correlation between the AUC FEV₁ and baseline FEV₁ ($r = 0.7$, $P = 0.2$).

Table 2

Mean (SD) area under the time–response curve (AUC) for FEV₁ and the systemic measurements, made at intervals over 4 h for each rac-formoterol dose

	FEV ₁ (mm h ⁻¹)	SpO ₂ (ml h ⁻¹)	Dyspnoea (% h ⁻¹)	HR (mm h ⁻¹)	Tremor (bpm h ⁻¹)	VAS tremor (m s ⁻¹ s ⁻¹ h ⁻¹)	SBP (mmHg h ⁻¹)	DBP
Placebo	–104.3 (59)	0.5 (0.2)	–25 (12)	–8.9 (2.3)	–0.42 (0.1)	–3.2 (2.1)	–21 (5)	–6.7 (3)
6 µg	225.3† (50)	1.2 (0.5)	–46.0 (15)	–2.8 (0.8)	–0.26 (0.1)	–4.6 (3.0)	–3.3 (2)	1.5 (1)
12 µg	362† (101)	0.3 (0.2)	–38.2 (19)	–2.5 (0.8)	–0.12 (0.05)	–20.7 (7.0)	–4.1 (2)	3.1 (2)
24 µg	510.8† (299)	–1.0 (0.2)	–46.2 (28)	–6.3 (2.3)	0.57† (0.2)	0.6 (10)	8.2 (3)	3.6 (2)
48 µg	626.6† (297)	1.1 (0.4)	–44.3 (19)	0.6† (3.3)	0.85† (0.4)	1.5 (5)	3.9 (3)	8.4 (5)
P-value	0.04*	0.69	0.98	0.65	<0.001*	0.04*	0.6	0.68

*P = 0.05 for dose–response trend. †P = 0.05 for individual rac-formoterol dose vs. placebo. FEV₁, forced expiratory volume in 1 s; HR, heart rate; VAS, visual analogue scale.

Tremor (Figures 1 and 2) Tremor measured by accelerometer increased with the two highest rac-formoterol doses compared with placebo and AUC tremor showed a dose–response effect. Tremor measured by VAS was more variable. Although there were no differences between individual doses and placebo, a dose–response relationship was present.

Heart rate (Figures 1 and 2) Mean heart rate fell after the three lowest doses of rac-formoterol and placebo, but rose following the highest (48 µg) dose of rac-formoterol, and this differed significantly from placebo. There was no difference between placebo and other rac-formoterol doses and no dose–response relationship.

Other end-points (Figures 1–3) The following end-points showed no difference between individual doses and placebo and no dose–response relationship: dyspnoea, oxygen saturation, systolic and diastolic blood pressure, ectopic beat rate, walk distance and plasma potassium levels. For example, the maximum change in 6-min walk distance between placebo and any dose of formoterol was around 15 m, which is less than 5% of the mean baseline walk distance of 360 m.

Satisfaction scores (Figure 3) Each rac-formoterol dose produced higher satisfaction scores than placebo, but with no dose–response relationship.

Adverse events

No serious adverse effects were reported during the study. Two individuals reported headache after placebo and rac-formoterol 6 µg, respectively, and one reported light-headedness 2 h after rac-formoterol 6 µg.

Discussion

In subjects with moderately severe, symptomatic COPD, rac-formoterol produced a dose-dependent increase in FEV₁ without a corresponding improvement in dyspnoea or walk distance. Tremor also increased in a dose-dependent manner, whereas heart rate increased significantly only after the highest dose. There was no significant effect on plasma potassium, blood pressure, oxygen saturation or ectopic beat rate. All doses of rac-formoterol produced higher satisfaction scores than placebo, although no dose–response relationship was evident.

Satisfaction with any treatment depends on the balance between beneficial and adverse effects. This is particularly relevant in COPD, where the largely irreversible nature of the disorder will limit the beneficial effects seen with higher drug doses, whereas adverse effects can continue to increase. The increase in FEV₁ in this study was small and of similar magnitude to that seen in other studies in subjects with COPD [14]. However, it was not associated with a significant reduction in dyspnoea scores or increase in exercise tolerance. This is consistent with previous studies with rac-formoterol and rac-salmeterol [4, 15] and presumably reflects, in part at least, the relatively small increase in FEV₁ seen in patients with COPD.

The adverse systemic effects of β₂-agonists are well known, but in this study only tremor and heart rate increased significantly with high doses of rac-formoterol. Moderate doses of rac-formoterol have been shown to increase heart rate, systolic blood pressure and QT interval, and to reduce plasma potassium and diastolic blood pressure in healthy volunteers [16–18]. The effects have been less marked in subjects with asthma [18–23], probably reflecting the development of tolerance [24–26]. Tolerance could also explain the limited systemic effects in our study, since all but one subject were taking β₂-agonists regularly.

Figure 1

Mean values over 240 min for forced expiratory volume in 1 s (FEV₁) (l), heart rate (bpm), S_pO₂ (%), dyspnoea visual analogue scale (VAS) (mm), tremor acceleration (m s⁻¹ s⁻¹), tremor VAS (mm), systolic (SBP) and diastolic blood pressure (DBP) (mmHg) after rac-formoterol 6 (▲), 12 (▼), 24 (◆) and 48 (●) µg and placebo (□)

We have summarized our findings as mean values, and as area under the curve for the measurements that were made on several occasions. Outliers may not be apparent with this approach, but could be important in relation to adverse effects. Checking individual data showed that the data were homogeneous and that there were no worrying outlying results. We limited the study to 4 h so that

responses would not be affected by meals, as in previous studies [16]. The greatest pharmacodynamic changes are known to occur within 4 h, so it is unlikely that additional effects after this time period were missed [16].

The dose-related increase in FEV₁ and limited systemic effects suggest that rac-formoterol may be suitable for use as rescue medication in COPD. Patients with COPD have an

Figure 2

The relationship between log dose rac-formoterol (μg) and mean area under the curve for forced expiratory volume in 1 s (FEV_1) (ml h^{-1}), heart rate (bpm h^{-1}), SpO_2 ($\% \text{ h}^{-1}$), dyspnoea visual analogue scale (VAS) (mm h^{-1}), tremor acceleration ($\text{m s}^{-1} \text{ s}^{-1} \text{ h}^{-1}$), tremor VAS (mm h^{-1}), systolic (SBP) and diastolic blood pressure (DBP) (mmHg h^{-1}) with placebo (P) shown for comparison ($\square$)

increased incidence of ischaemic heart disease, however, and therefore greater potential for cardiac arrhythmias. In a small study in subjects with COPD and a previous cardiac arrhythmia, rac-formoterol 24 μg caused a greater effect on heart rate, plasma potassium, supraventricular and ventricular premature beats than the 12- μg dose [27]. There was a trend towards increased ectopic beats with higher doses in our study, but a larger long-term study would be needed to assess fully the safety of higher doses in these patients.

Assessing the balance between beneficial and adverse effects is difficult, and asking about overall satisfaction with the drug after each study day was an attempt to address the patients' perception of this balance. Satisfaction scores are difficult to validate, but formoterol produced greater subject satisfaction than placebo in keeping with its effect on FEV_1 , and a similar approach had face validity in our previous study [28]. This study compared different doses of rac-salbutamol in subjects with COPD

Figure 3

The relationship between log dose rac-formoterol (μg) and change in 6-min walk distance (m), change in plasma potassium concentration (mmol l^{-1}), mean rate of ventricular ($\blacktriangle$) and supraventricular ($\blacksquare$) ectopic beats and mean satisfaction scores (mm), with placebo (P) shown for comparison ($\square$)

and found a bell-shaped response, in that subjects preferred a modest dose of rac-salbutamol (1 mg) to both placebo or the highest dose (4 mg), presumably because the 1-mg dose offered the best balance between beneficial and adverse effects. Satisfaction improved with all doses of rac-formoterol in the current study, however, suggesting that the perceived adverse effects of 48 μg did not exceed the perceived benefit.

Inhaled rac-formoterol up to 48 μg produced a dose-dependent improvement in FEV_1 with few systemic effects in subjects with moderate to severe COPD. Satisfaction scores were higher with all doses of rac-formoterol. Further studies are warranted to determine whether rac-formoterol has a useful role as rescue medication for patients with COPD.

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Competing Interests: CIW and MPS have received financial support from AstraZeneca to attend meetings. MPS's salary was from a non-conditioned grant from AstraZeneca for a different study. AET and TWH have received honoraria from AstraZeneca for speaking at meetings and TWH received honoraria for being on advisory groups. HJM has no competing interests to declare.

REFERENCES

- 1 Dahl R, Greenhorst LAPM, Nowak D, Nonikov V, Byrne AM, Thomson MH, Till D, Della Cioppa G. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 778–84.
- 2 D'Urzo AD, Cristina De Salvo M, Ramirez-Rivera A, Almeida J, Sichletidis L, Rapatz G, Kottakis J. In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium. *Chest* 2001; 119: 1347–56.
- 3 National Institute of Clinical Excellence. Chronic Obstructive Pulmonary Disease. Management of Chronic Obstructive Pulmonary Disease in adults in primary and secondary care. Clinical Guideline 12. 2004. Available at <http://www.nice.org.uk/CG012NICEguidelines> (last accessed: January 2007).
- 4 Aalbers R, Ayers J, Backer V, Decramer M, Lier PA, Magyar P, Malolepszy J, Ruffin R, Sybrecht GW. Formoterol in patients with chronic obstructive pulmonary disease: a randomised, controlled, 3-month trial. *Eur Respir J* 2002; 9: 178–85.
- 5 Cazzola M, Grella E, Matera MG, Mazzarella G, Marsico SA. Onset of action following formoterol Turbuhaler and salbutamol pMDI in reversible chronic airway obstruction. *Pulm Pharmacol Ther* 2002; 15: 97–102.
- 6 Cazzola M, Centanni S, Regorda C, di Marco F, di Perna F, Carlucci P, Boveri B, Santus P. Onset of action of single doses of formoterol administered via Turbuhaler in patients with stable COPD. *Pulm Pharmacol Ther* 2001; 14: 41–5.
- 7 Tattersfield AE, Lofdahl C-G, Postma DS, Eivindson A, Schreurs AGM, Rasidakis A, Ekstrom T. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001; 357: 257–61.
- 8 Campbell M, Eliraz A, Johansson G, Tornling G, Nihlen U, Bengtsson T, Rabe KF. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 1511–20.
- 9 Schmekel B, Borgstrom L, Wollmer P. Difference in pulmonary absorption of inhaled terbutaline in healthy smokers and non-smokers. *Thorax* 1991; 46: 225–8.
- 10 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–7.
- 11 Sciruba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA. Six-minute walk distance in chronic obstructive pulmonary disease. Reproducibility and effect of walking course layout and length. *Am J Crit Care Med* 2003; 167: 1522–7.
- 12 Tweeddale PM, Alexander F, McHardy GJ. Short term variability in FEV₁ and bronchodilator responsiveness in patients with obstructive ventilatory defects. *Thorax* 1987; 42: 487–90.
- 13 Bennett JA, Smyth ET, Pavord ID, Wilding PJ, Tattersfield AE. Systemic effects of salbutamol and salmeterol in patients with asthma. *Thorax* 1994; 49: 771–4.
- 14 Cazzola M, Matera M, Santangelo G, Vinciguerra A, Rossi F, D'Amato G. Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose-response study. *Respir Med* 1995; 89: 357–62.
- 15 Boyd G, Morice AH, Poundsford JC, Siebert M, Peslis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 815–21.
- 16 Guhan AR, Cooper S, Osborne J, Lewis S, Bennett J, Tattersfield AE. Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects. *Thorax* 2000; 55: 650–6.
- 17 Bremner P, Woodman K, Burgess C, Crane J, Purdie G, Pearce N, Beasley R. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J* 1993; 6: 204–10.
- 18 Rosenborg J, Bengtsson T, Larsson P, Blomgren A, Persson G, Lotvall J. Relative systemic dose potency and tolerability of inhaled formoterol and salbutamol in healthy subjects and asthmatics. *Eur J Clin Pharmacol* 2000; 56: 363–70.
- 19 Totterman K, Huhti L, Sutinen E, Backman R, Pietinalho A, Falck M, Larsson P, Selroos O. Tolerability to high doses of formoterol and terbutaline via Turbuhaler for 3 days in stable asthmatic patients. *Eur Respir J* 1998; 12: 573–9.
- 20 Burgess C, Ayson M, Rajasingham S, Crane J, Della Cioppa G, Till MD. The extrapulmonary effects of increasing doses of formoterol in patients with asthma. *Eur J Clin Pharmacol* 1998; 54: 141–7.
- 21 Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med* 1999; 160: 244–9.
- 22 Maesen FPV, Costongs R, Smeets JJ, Brombacher PJ, Zweers PGMA. The effect of maximal doses of formoterol and salbutamol from a metered dose inhaler on pulse rates, ECG, and serum potassium concentrations. *Chest* 1991; 99: 1367–73.
- 23 Malolepszy J, Boszormenyi Nagy G, Selroos O, Larsson P, Brander R. Safety of formoterol Turbuhaler at cumulative dose of 90 µg in patients with acute bronchial obstruction. *Eur Respir J* 2001; 18: 928–34.
- 24 Harvey JE, Baldwin CJ, Wood PJ, Alberti KGMM, Tattersfield AE. Airway and metabolic responsiveness to intravenous salbutamol in asthma: effect of regular inhaled salbutamol. *Clin Sci* 1981; 60: 579–85.
- 25 Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high dose inhaled salbutamol in asthmatics. *Am Rev Respir Dis* 1989; 140: 586–92.
- 26 O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2 -agonists in asthma. *N Engl J Med* 1992; 327: 1204–8.
- 27 Cazzola M, Imperatore F, Salzillo A, Di Perna F, Calderaro F, Imperatore A, Matera MG. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxaemia. *Chest* 1998; 114: 411–5.
- 28 Vathenen AS, Britton JR, Ebdon P, Cookson JB, Wharrad HJ, Tattersfield AE. High dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988; 138: 850–5.