Salmeterol xinafoate in the treatment of mild to moderate asthma in primary care

K P Jones, on behalf of a UK study group

Abstract

Background – Clinical studies of inhaled salmeterol xinafoate have been conducted mainly in moderately to severely affected asthmatic subjects in hospital settings. This study was conducted to investigate the effectiveness of this drug in patients with milder asthma in primary care.

Methods – A multicentre, double blind, randomised, parallel group comparison of salmeterol xinafoate in a dose of 50 µg twice daily with placebo, both administered from a four-place dry powder inhaler (Diskhaler), was performed over six weeks in United Kingdom general practices.

Results – A total of 427 asthmatic patients aged 18 years or older were randomised to receive salmeterol or placebo in a 2:1 ratio. Of the total randomised population, 247 patients were previously on short acting bronchodilators alone whilst 180 patients were concurrently receiving up to 400 µg inhaled corticosteroid. Mean morning peak expiratory flow rose more in the salmeterol group than in the placebo group (treatment difference 17 l/min, 95% confidence interval 9 to 26 l/min) but there was a smaller, non-significant difference in mean evening peak expiratory flow. Improvements occurred in the salmeterol-treated group compared with placebo for wheeze, shortness of breath, undisturbed nights, and relief medication use, irrespective of concomitant inhaled corticosteroid use. In addition, improvement in activity restriction was seen in the salmeterol group compared with placebo in the subgroup receiving only bronchodilator.

Conclusions – Salmeterol is effective and well tolerated in the short term in mildly asthmatic adult patients irrespective of concomitant use of inhaled corticosteroid therapy.

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included patients with moderate or severe disease, and there have been few trials of asthmatic patients at the milder end of the spectrum.⁸

The use of regular short acting inhaled β_2 agonist treatment alone is not in accord with the current British Thoracic Society guidelines.⁹ Despite the continuing discussion concerning the use of this regimen,¹⁰⁻¹³ some primary care physicians still use such treatment in mild asthmatic patients. Others may use this approach in patients on low dose inhaled steroids.

This study therefore sought to assess the effect in primary care of adding inhaled salmeterol to the treatment of mild adult asthmatic patients previously receiving either inhaled short acting bronchodilators alone, or with inhaled corticosteroids at low doses only.

Methods

STUDY DESIGN

This multicentre, double blind, placebo controlled, parallel group comparison was conducted with a two week baseline period, a six week treatment period, and a two week follow up period. Five visits to the surgery were made during this period (weeks 0, 2, 4, 8, and 10). Asthmatic patients entering the baseline phase of the study had to be aged 18 years or over and had to have requested a minimum of one and a maximum of four prescriptions for a 200 dose salbutamol metered dose inhaler (or its equivalent in other delivery devices) in the four months prior to their entry. They also had to demonstrate correct use of the Diskhaler. The study population consisted of patients with mild asthma on inhaled β_2 agonists alone or inhaled β_2 agonists plus inhaled corticosteroid at doses up to 400 µg daily via a metered dose inhaler (or equivalent). On entry, any bronchodilators currently being used were withdrawn and replaced by salbutamol (400 µg per dose) via the eight place Diskhaler for use as required. Those patients already receiving inhaled corticosteroids continued with this therapy. No other anti-asthma medication was permitted during the course of the study.

During the two week baseline period, patients completed a daily diary assessing symptoms of cough, wheeze, and shortness of breath on a four point scale: 0 = no symptoms, 1 = symptoms for one short period, 2 = symptoms for two or more short periods, and 3 = symptoms for most of the day or night. On a daily basis, patients also recorded waking during the previous night, activity restriction, and use of relief medication throughout the day. Morning and evening peak expiratory flow (PEF) measurements (best of three blows) were

Department of
Primary Medical
Care, University of
Southampton
K P Jones

Reprint requests to:
Dr K P Jones, Department
of Primary Health Care, The
Medical School, Newcastle
upon Tyne NE2 4HH, UK.

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Salmeterol xinafoate was introduced for clinical use in adult asthmatic patients in the United Kingdom in December 1990. It represents the first in a new class of long acting, inhaled β_2 agonist bronchodilators.¹ Its bronchodilator effect is similar to that of salbutamol, although its duration of action is longer.² Clinical studies have so far shown its effectiveness in improving lung function and reducing symptoms, particularly at night.³⁻⁷ Most studies to date have

Table 1 Demographic details

	Bronchodilator only subgroup		Corticosteroid users subgroup		Total population	
	Salmeterol (n = 162)	Placebo (n = 85)	Salmeterol (n = 120)	Placebo (n = 60)	Salmeterol (n = 282)	Placebo (n = 145)
Sex						
Male	83	49	53	22	136	71
Female	79	36	67	38	146	74
Age (years)						
Mean	35.8	37.0	42.6	39.4	38.7	38.0
Range	(18.0–75.9)	(18.0–70.2)	(18.5–79.6)	(19.7–69.7)	(18.0–79.6)	(18.0–70.2)
Baseline PEF (l/min)						
Mean morning (% predicted)	395 (83.1)	416 (77.1)	391 (78.6)	357 (79.8)	394 (80.5)	391 (78.7)
Mean evening (% predicted)	425 (87.7)	442 (81.9)	413 (84.3)	378 (84.9)	420 (85.7)	415 (83.6)

PEF = peak expiratory flow.

also recorded, using the mini-Wright peak flow meter, before taking study medication on each occasion.

At the end of the baseline period patients who satisfied the following criteria proceeded to the next phase of the study: (1) a forced expiratory volume in one second (FEV₁) of at least 75% of predicted for sex, age, and height (without having used a bronchodilator in the previous four hours); (2) either reversibility in peak flow or FEV₁ of at least 15% to a salbutamol dry powder dose of 400 µg or a period variation in peak flow of at least 15% (calculated as the highest evening peak flow value minus the lowest morning value divided by the highest evening value, over at least 14 days, and expressed as a percentage); (3) symptoms on at least eight days of the baseline period; (4) use of relief medication on at least eight days of the baseline period. In addition, patients had to have clinically normal blood biochemistry (urea and electrolytes, liver function tests and lipids) and full blood count from samples taken at the first visit. FEV₁ was measured as the best of three attempts using a turbine spirometer (Micromed).

Eligible patients were randomised in a 2:1 ratio (in favour of salmeterol) to receive either salmeterol 50 µg twice daily via the four place Diskhaler or a matching placebo. Daily diary card recording of symptoms (as described previously), relief medication use, and morning and evening peak flow were continued throughout the study.

At the end of the treatment period patients were asked to rate the treatment as excellent, good, moderate, or poor whilst the physicians were asked to rate the treatment as either a success or a failure. Safety was assessed by recording any adverse events experienced by the patient, by checking standard biochemical and haematological parameters before and after the treatment period, and by taking spirometric measurements in the surgery. Spirometry was not used as an efficacy outcome because the interval between use of previous relief medication and time of surgery visit was not controlled at all visits.

The study was conducted under the Clinical Trials Exemption (CTX) procedure. Ethical approval was obtained from the ethics committee of Southampton and South West Hampshire Health Authority. This approval was used as the basis of approval for all investigating centres unless local approval was requested by individual investigators. Before entering the

study written witnessed informed consent was obtained from all patients.

SAMPLE SIZE

For the purpose of sample size calculations the primary variable of mean morning PEF was used. In order to have a 90% chance of detecting a 30 l/min difference in mean morning PEF between the two groups at the 5% level, a total of 340 patients were required; 113 to receive placebo and 227 to receive salmeterol xinafoate. This assumed a standard deviation of PEF of 80 l/min.

STATISTICAL METHODS

All analyses were conducted on SAS version 6.04,¹⁴ on an "intention to treat" basis, analysing the difference between salmeterol and placebo treatments using the second week of the run-in period as baseline and all but the first treatment week as the treatment period. Mean morning and mean evening PEF data were analysed using analysis of covariance (ANCOVA).

The Wilcoxon rank sum test was used in the analysis of the symptoms, use of relief medication, and undisturbed nights. A 5% two-tailed significance level was used for peak flow analysis as the main outcome variable and a 1% level for all other analyses. The main subgroup of interest was the population of patients who had previously used only bronchodilator therapy. For each variable a statistical test was carried out to assess whether there was homogeneity of treatment differences across the two subgroups. If there was no homogeneity – that is, a statistically significant result at the 10% level ($p=0.1$) between the subgroups – the variables were analysed separately for each of these subgroups. If homogeneity was found, the treatment difference of the variable was considered to be consistent between subgroups. Due to the nature of the various types of data, different models were used for testing homogeneity. For morning and evening PEF a linear model was employed, whilst for the proportion of symptom-free days and undisturbed nights a log linear model was used.

Results

DEMOGRAPHY

Six hundred and sixty nine patients were recruited into the study by 146 participating

Figure 1 Change from baseline for mean morning peak expiratory flow (PEF) plotted separately for both subgroups of the study population: □ salmeterol, ■ placebo (bronchodilator only subgroup); △ salmeterol, ▲ placebo (corticosteroid users).

Figure 2 Change from baseline for mean evening peak expiratory flow (PEF) plotted separately for both subgroups of the study population: □ salmeterol, ■ placebo (bronchodilator only subgroup); △ salmeterol, ▲ placebo (corticosteroid users).

Table 2 Surgery recordings of mean (SD) lung function data

	Salmeterol		Placebo	
	Baseline (n=282)	End of treatment (n=227)	Baseline (n=144)	End of treatment (n=120)
PEF (l/min)	416 (111)	446 (115)	417 (109)	436 (111)
FEV ₁ (litres)	2.66 (0.71)	2.70 (0.82)	2.69 (0.70)	2.62 (0.79)
FVC (litres)	3.20 (0.97)	3.27 (1.02)	3.27 (1.00)	3.30 (1.07)

PEF=peak expiratory flow; FEV₁=forced expiratory volume in one second; FVC=forced ventilatory capacity.

Table 3 Mean (SD) changes in parameters considered to be homogenous between the two subgroups ($p > 0.1$) for the proportion of undisturbed nights, proportion of days without relief medication, and proportion of days with no symptoms (score = 0) for total study population

	Salmeterol (n=282)		Placebo (n=145)		p
	Baseline	Treatment	Baseline	Treatment	
Undisturbed nights	0.77 (0.29)	0.85 (0.25)	0.80 (0.28)	0.82 (0.24)	<0.01
Without relief medication	0.06 (0.16)	0.36 (0.38)	0.07 (0.17)	0.21 (0.32)	<0.0005
Wheeze	0.37 (0.37)	0.55 (0.37)	0.39 (0.38)	0.51 (0.37)	<0.05
Shortness of breath	0.36 (0.37)	0.53 (0.38)	0.41 (0.38)	0.48 (0.37)	<0.0005

Table 4 Mean (SD) changes from baseline in parameters considered non-homogenous between the two subgroups ($p < 0.1$) of the study population

	Bronchodilator only subgroup (n=282)		Corticosteroid subgroup (n=180)	
	Salmeterol (n=162)	Placebo (n=85)	Salmeterol (n=120)	Placebo (n=60)
Free from activity restriction	0.07 (0.23)*	-0.02 (0.12)	-0.02 (0.17)	0.03 (0.19)
Coughing	0.13 (0.33)	0.04 (0.31)	0.05 (0.30)	0.07 (0.37)

* $p < 0.005$ compared with placebo group. All other comparisons non-significant.

general practitioners throughout the UK; 242 did not meet the criteria for continuing past the second visit, resulting in 282 being randomised to receive salmeterol and 145 to receive placebo. These patients were distributed between the two subgroups as follows: (1) 180 (42%) had received inhaled corticosteroids in the four months before the study (120 were randomised to receive salmeterol and 60 to placebo); (2) 247 patients had previously used bronchodilator only (162 of these received salmeterol and 85 received placebo).

The study population within each treatment group was similar in demography although across the subgroups there were some distinct differences (table 1). There were proportionally more men than women in the bronchodilator only subgroup, whereas the opposite was true in the corticosteroid treatment group. Additionally, there were more patients with asthma classed as "moderate" in the corticosteroid subgroup (61%) than in the bronchodilator only subgroup (36%). This is also reflected in the higher mean PEF values at baseline seen in the bronchodilator only subgroup (table 1).

In total, 85 patients withdrew during the study, including 28 patients who were withdrawn when the investigator realised they were ineligible for the study on the basis of the pretreatment data. Of the 85 withdrawn patients, 57 withdrew from the salmeterol group and 28 from the placebo group. In 34 cases the main reason given was an adverse event (22 on salmeterol and 12 on placebo). This was similar in both treatment groups, considering the 2:1 ratio of treatment allocation.

EFFICACY RESULTS

Lung function

Over the whole treatment period patients treated with salmeterol had a statistically significant improvement in morning peak flow (taken before the morning medication) compared with the placebo-treated patients ($p < 0.0001$), the mean difference being 17 l/min (95% confidence interval (95% CI) 9 to 26 l/min). There was a smaller, non-significant improvement in evening PEF in salmeterol-treated patients. Figures 1 and 2 show the weekly changes from baseline in morning and evening PEF. These results were not influenced by the concomitant use of inhaled corticosteroids ($p > 0.1$ between subgroups). Surgery recordings of lung function data are shown in table 2.

Symptom scores

In the total population there were statistically significant improvements in the patients treated with salmeterol compared with those on placebo in the proportion of days without wheeze ($p < 0.05$), without shortness of breath ($p < 0.0005$), and without relief medication ($p < 0.0005$) (table 3). Additionally, the proportion of undisturbed nights was significantly greater in the salmeterol-treated patients than

Table 5 Number (%) of adverse events for the total study population during the treatment period

Adverse events	Salmeterol (n=282)		Placebo (n=145)	
	Serious*	Minor	Serious*	Minor
Respiratory disorders	16 (6)	45 (16)	8 (6)	16 (11)
Blood disorders	14 (5)	3 (1)	10 (7)	0 (0)
Nervous system disorders	7 (2)	19 (8)	1 (<1)	15 (10)
Digestive disorders	4 (1)	3 (1)	0 (0)	3 (2)
Skin disorders	0 (0)	1 (<1)	5 (3)	0 (0)
Others	3 (1)	7 (2)	2 (1)	16 (11)
Total number of reports	44 (16)	78 (28)	26 (18)	50 (34)
Total number of patients	31 (11)	43 (15)	17 (12)	27 (17)

*Includes any event leading to withdrawal of study medication.

those receiving placebo ($p<0.01$) (table 3). However, there was no difference between the two subgroups in any of these parameters, although they did differ in the proportion of days free from activity restriction. A significant increase in the proportion of days free from activity restriction was reported for the salmeterol-treated patients compared with placebo within the bronchodilator only subgroup ($p<0.005$) which was not seen in the subgroup of patients who were using corticosteroids (table 4). Neither subgroup showed any significant response in the proportion of days free from coughing (table 4).

Patient and physician assessments

Overall, where ratings were given, treatment with salmeterol was rated by the investigator as a success in 184/231 (80%) of patients compared with 74/123 (60%) on placebo ($p<0.0005$). Likewise, 168 (73%) of patients rated their improvement on salmeterol as excellent or good, compared with 61 (50%) on placebo ($p<0.0005$). Only 17 (7%) salmeterol-treated patients and 12 (10%) patients taking placebo regarded the treatments as poor.

SAFETY RESULTS

One hundred and seventy nine patients reported one or more minor adverse events during the treatment phase of the study, 119 (42%) on salmeterol and 60 (41%) on placebo. Respiratory system disorders were reported most frequently followed by nervous system and digestive system disorders (table 5). Thirty one patients (11%, 44 reports) experienced an adverse event classified as serious (including any event leading to the withdrawal of study medication) during salmeterol treatment in the total study population, compared with 17 patients (12%, 25 reports) in the placebo group (table 5). The numbers of patients who withdrew due to adverse events related to asthma were similar in both groups (eight (3%) in the salmeterol group and six (4%) in the placebo group).

Any haematological or biochemical blood parameter outside the normal range at the end of treatment considered to be clinically significant (with or without associated symptoms) was classified as serious. Of the 14 abnormal blood reports (5%) at the end of salmeterol treatment only four were considered by the investigator as "probably" related to study medication. In the placebo group there were 10 (7%) abnormal blood results of which two

were assessed as "probably" related to the study medication. It should be noted that no one parameter was consistently abnormal and, moreover, with the reports considered "probable" no one value was greatly outside the normal range, no clinical symptoms were reported, and no medical intervention was required.

Discussion

The addition of regular salmeterol produced significant improvements in both lung function and symptomatology despite the mild nature of the asthma exhibited by the subjects in this study. Salmeterol-treated patients reported a reduction in the use of relief medication, increased number of days free from wheeze and shortness of breath, as well as an increase in the number of undisturbed nights. These improvements were irrespective of the concomitant use of inhaled corticosteroids – a result consistent with a previous study that included cohorts of patients treated with corticosteroids and bronchodilators only within the study population.¹⁵

Our cohort of asthmatic adults was indeed mildly affected by their disease. At baseline they had about 80% of days and nights undisturbed, and mostly no or few daily symptoms. The main indicator that patients were symptomatic during the baseline period came from the use of relief bronchodilator. Irrespective of the concomitant use of corticosteroids, patients required relief medication almost every day in the baseline period.

During the past few years there have been a number of consensus statements concerning the management of asthma in both adults and children.^{9,16–20} In the UK the British Thoracic Society guidelines on the management of chronic asthma⁹ emphasise a stepwise approach to treatment with regular inhaled anti-inflammatory medications for any patient with nocturnal symptoms and/or those needing to use bronchodilators more than once daily.

The protocol for the present study was set up not only before publication of the original British Thoracic Society guidelines,²⁰ but also with the prior advice of the investigators who felt that insufficient patients on bronchodilators alone meeting protocol criteria would be found in general practice. The fact that so many subjects on inhaled bronchodilators alone were actually found in practices with some special interest in asthma is in itself an interesting result and supports the importance of establishing management guidelines in the UK. The majority of asthmatic patients in the UK are cared for entirely in general practice,^{21,22} and several community surveys have established the burden of asthma which continues to be suffered by such patients.^{23–26} We have chosen to investigate subjects who would be classified as mild on lung function data ($FEV_1 >75\%$ of predicted) and who request no more than one metered dose inhaler for bronchodilator therapy per month. Many of these would now be eligible on the British Thoracic Society criteria to receive inhaled corticosteroids (if not already on them),

but previously may not have been so considered.

Since the availability of salmeterol there has been considerable debate concerning the appropriate place for the drug in the stepwise approach originally suggested by the British Thoracic Society.²⁰ This process has been made more complex by recent discussions concerning the use of β_2 agonist bronchodilators in general.²⁷ This present study therefore provides part of the further evidence needed to establish fully the role of salmeterol in asthma treatment.

It provides reassurance that salmeterol can improve lung function and relieve symptoms even in those patients considered by their general practitioners to have mild asthma who receive only short acting bronchodilators on an "as required" basis. The lack of improvement in cough symptoms was interesting and suggests that salmeterol was acting primarily as a bronchodilator. The comparative improvements were modest but clinically significant considering the mild nature of the asthma suffered, with 60% of subjects on placebo thought to be improved by their clinicians, compared with 80% of subjects on salmeterol. The safety profile of regular twice daily salmeterol in this short term study was not different from that of the short acting bronchodilator used as relief medication by the placebo group, although it would need to be confirmed that this was maintained in longer term studies. Some confirmatory evidence has been provided in a 12 month study comparing salmeterol and salbutamol, where the improvements in lung function and control of asthma were maintained with salmeterol throughout the study period.^{8,28} The finding by Cheung *et al* that regular treatment of patients with mild asthma with salmeterol leads to a degree of tolerance to its protective effects against inhaled methacholine does, however, urge some caution in this regard.²⁹ However, this is in contrast to a recent study by Booth *et al* which found no evidence of tachyphylaxis to methacholine challenge following eight weeks of regular treatment with salmeterol.³⁰

Salmeterol is clearly both effective and well tolerated in the short term in mild asthmatic patients. Because of the discussion on the regular use of short acting, inhaled β_2 agonists in general, and the need for more clinical evidence on any additional effects of salmeterol, it is clearly not appropriate at the present time to recommend the use of this drug in place of or before that of inhaled corticosteroids. However, it would be useful to investigate the comparative effects of using either salmeterol or an inhaled corticosteroid in such mildly affected patients over a longer time period.

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- 1 Lofdahl CG, Chung KR. Long acting beta₂-adrenoceptor agonists: a new perspective in the treatment of asthma. *Eur Respir J* 1991;4:218-26.
- 2 Ullman A, Svedmyr N. Salmeterol, a new long-acting inhaled beta₂-adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. *Thorax* 1988;43: 674-8.
- 3 Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. *Am Rev Respir Dis* 1990; 142:571-5.
- 4 Britton M. Salmeterol and salbutamol: large multicentre studies. *Eur Respir J* 1991;1:288-92.
- 5 Fjellbirkeland L, Gulsvik A. Salmeterol and theophylline sustained release: a crossover comparison in asthmatic patients. *Clin Exp Allergy* 1990;20(Suppl 1):94.
- 6 Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double-blind placebo-controlled trial of a long-acting inhaled beta₂-agonist. *BMJ* 1990;301:1365-8.
- 7 Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airway disease. *Eur Respir J* 1991; 4:1174-80.
- 8 Lundback B, Rawlinson DW, Palmer JBD. Twelve month comparison of salmeterol and salbutamol as dry powder formulations in asthmatic patients. *Thorax* 1993;43:148-53.
- 9 British Thoracic Society and others. Guidelines on the management of asthma. *Thorax* 1993;48(Suppl):1-24.
- 10 Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, *et al*. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
- 11 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, *et al*. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326:501-6.
- 12 Rees J. Beta₂-agonists and asthma: still the mainstay of symptomatic treatment. *BMJ* 1991;302:1166-7.
- 13 Committee on Safety of Medicines. Beta-agonist use in asthma. Report from the CSM Working Party. *Current Problems* February 1992; No 33.
- 14 SAS Institute Inc. SAS/STAT TM. Guide for Personal Computers, Version 6 Edition. Cary, NC: SAS Institute, 1987:1028pp.
- 15 Pearlman DS, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP, *et al*. A comparison of salmeterol with albuterol in the treatment of mild to moderate asthma. *N Engl J Med* 1992;327:1420-5.
- 16 Sheffer AL (chairman). International consensus report on diagnosis and treatment of asthma. *Clin Exp Allergy* 1992; 22(Suppl 1):1-72.
- 17 Sheffer AL (Chairman). Guidelines for the diagnosis and management of asthma. National Heart, Lung and Blood Institute national asthma education program expert panel report. *J Allergy Clin Immunol* 1991;88:425-534.
- 18 Warner JO, Gotz M, Landau LI, Levison H, Milner AD, Pedersen S, *et al*. Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.
- 19 Asthma: a follow-up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992;67: 240-8.
- 20 Guidelines for management of asthma in adults: I - Chronic persistent asthma. *BMJ* 1990;301:651-3.
- 21 Charlton IH, Bain J. The care of children with asthma in general practice: signs of progress? *Br J Gen Pract* 1991; 41:256.
- 22 Neville RG, Clark RC, Hoskins G, Smith B, for the General Practitioners in Asthma Group. National asthma attack audit 1991-2. *BMJ* 1993;306:559-62.
- 23 White PT, Pharoah CA, Anderson HR, Freeling P. Randomized controlled trial of small group education on the outcome of chronic asthma in general practice. *J R Coll Gen Pract* 1989;39:182-6.
- 24 Turner-Warwick M. Nocturnal asthma: a study in general practice. *J R Coll Gen Pract* 1989;39:239-43.
- 25 Horn CR, Cochrane GM. An audit of morbidity associated with chronic asthma in general practice. *Respir Med* 1989; 83:71-75.
- 26 Jones KP, Bain DJG, Middleton M, Mullee MA. Correlates of asthma morbidity in primary care. *BMJ* 1992;304: 361-4.
- 27 Lofdahl CG, Svedmyr N. Beta-agonists - friends or foes? *Eur Respir J* 1991;4:1161-5.
- 28 Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992;5:1062-7.
- 29 Cheung D, Timmers MC, Zuiderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta₂-adrenoceptor agonist, salmeterol, on airway hyper-responsiveness in patients with mild asthma. *N Engl J Med* 1992;327:1198-203.
- 30 Booth H, Fishwick K, Harkawat R, Devreux G, Hendrick DJ, Walters E. Changes in methacholine induced bronchoconstriction with the long acting β_2 agonist salmeterol in mild to moderate asthmatic patients. *Thorax* 1993;48: 1121-4.