

Effects of corticosteroids on bronchodilator action in chronic obstructive lung disease

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Abstract

Background Short term treatment with corticosteroids does not usually reduce airflow limitation and airway responsiveness in patients with chronic obstructive lung disease. We investigated whether corticosteroids modulate the effects of inhaled salbutamol and ipratropium bromide.

Methods Ten non-allergic subjects with stable disease were investigated; eight completed the randomised, double blind, three period cross over study. Treatment regimens consisted of 1.6 mg inhaled budesonide a day for three weeks, 40 mg oral prednisone a day for eight days, and placebo. After each period cumulative doubling doses of salbutamol, ipratropium, a combination of salbutamol and ipratropium, and placebo were administered on separate days until a plateau in FEV₁ was reached. A histamine challenge was then performed.

Results At the end of placebo treatment mean FEV₁ was 55.5% predicted after inhaled placebo, 67.9% predicted after salbutamol and 64.0% predicted after ipratropium. Compared with the results after the placebo period the FEV₁ with salbutamol increased by 0.7% predicted after treatment with budesonide and by 0.7% predicted after treatment with prednisone; the FEV₁ with ipratropium increased by 0.7% predicted after budesonide and by 4.8% predicted after prednisone; none of these changes was significant. After placebo treatment the geometric mean PC₂₀ was 0.55 mg/ml after placebo, 1.71 mg/ml after salbutamol and 0.97 mg/ml after ipratropium. Compared with the placebo period the PC₂₀ with salbutamol was increased by 0.86 doubling concentrations after treatment with budesonide, and by 0.67 doubling concentrations after prednisone; the PC₂₀ with ipratropium increased by 0.03 and 0.34 doubling concentrations after budesonide and after prednisone respectively compared with placebo; none of these changes was significant.

Conclusions In non-allergic subjects with chronic obstructive lung disease short term treatment with high doses of inhaled or oral corticosteroids does not modify the bronchodilator response to

salbutamol or ipratropium or the protection provided by either drug against histamine. Salbutamol produces greater protection from histamine induced bronchoconstriction than ipratropium.

Corticosteroids have been shown to improve symptoms, lung function, and airway responsiveness in subjects with asthma.¹⁻³ The effects of oral and inhaled corticosteroids in patients with chronic obstructive lung disease are less clear,⁴⁻¹⁰ perhaps partly because of heterogeneity among these patients. Previous studies of corticosteroid treatment in patients with chronic obstructive lung disease have looked mainly at changes in airflow limitation and airway responsiveness. In some studies corticosteroids produced no benefit^{7,9} whereas in others benefit was seen in patients with atopy and eosinophilia^{4,6} or reversible airflow limitation.⁵ It has been suggested that corticosteroids, apart from an effect on lung function, may influence the effects of a bronchodilator as they potentiate the response to β agonists in asthmatic^{10,11} and normal subjects.¹² The combination of a corticosteroid and an anticholinergic agent was more effective in subjects with asthma than either drug alone, but this was not the case in patients with chronic bronchitis.¹³ The aim of the present study was to investigate whether the effects of β adrenergic and anticholinergic bronchodilators are modified by treatment with corticosteroids in non-allergic subjects with stable chronic obstructive lung disease. The effects of cumulative doubling doses of salbutamol and ipratropium on airflow limitation and airway responsiveness were studied after treatment with high dose oral and inhaled corticosteroids.

Methods

PATIENTS

Eight men and two women, aged 49 to 66 years, were examined after giving informed consent. All patients had dyspnoea continuously or on exertion and were current or former smokers. None had a history of attacks of wheezing and dyspnoea consistent with asthma. All were clinically stable with no respiratory infection or exacerbation in the two months before the study. Patients were selected only if they had negative skin test results for common inhaled allergens, normal concentrations of total IgE, a baseline forced expiratory volume in one second (FEV₁) of 40-80% of the predicted

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value (% predicted),¹⁴ and a provocation concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) of less than 8 mg/ml. The study was approved by the hospital medical ethics committee.

PROTOCOL

When subjects came to the lung function laboratory for assessment they had taken no inhaled corticosteroid for six weeks and no bronchodilator except for β agonists for two weeks. Spirometry and a histamine challenge test were performed. Subjects then entered a double blind, randomised, cross over study consisting of three treatment periods of three weeks, each of which was followed by four study days. During each treatment period patients received four puffs twice daily by metered dose inhaler with a spacing device (Spacer, Astra-Draco, Lund, Sweden) for three weeks and four tablets twice daily for the last eight days. The treatment regimens were (a) inhaled budesonide (1.6 mg daily) and placebo tablets; (b) inhaled placebo and prednisone tablets (40 mg daily); and (c) inhaled placebo and placebo tablets. The study treatment was continued during the four study days. Inhaler technique was checked on every visit. Inhaled salbutamol was allowed if required during the study except in the 12 hours before the start of the measurements.

On the four study days after each treatment period the airway response to cumulative doubling doses of bronchodilators was measured. Bronchodilator solutions contained ipratropium, salbutamol, a combination of the two drugs, or saline, and were administered by nebuliser in a double blind, randomised and cross over design.

SPIROMETRY AND HISTAMINE RESPONSIVENESS

FEV₁ was measured with a water sealed spirometer (Lode BV, Groningen, Netherlands), the best of three attempts being accepted. Bronchial challenge tests were performed by the method described by Cockcroft *et al*¹⁵ with a De Vilbiss 646 nebuliser (De Vilbiss, Somerset, United States) with an output of 0.13 ml/min. A 0.9% phosphate buffered saline solution and doubling histamine diphosphate concentrations from 0.03 to 16 mg/ml were inhaled for two minutes at five minute intervals until the FEV₁ had fallen by 20% from the value obtained after inhaling saline. The provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) was calculated by interpolation of the last two points of the log dose-response curve. Values above 8 mg/ml were considered to be normal. If the PC₂₀ was greater than 16 mg/ml an extrapolation was performed from the last two points of the curve. If the PC₂₀ was greater than 32 mg/ml a PC₂₀ value of 64 mg/ml was assigned.

BRONCHODILATOR ASSESSMENT

Patients were studied at 8 to 8.30 am after 15 minutes' rest, provided that the baseline FEV₁ on days 2-4 was within 10% of the FEV₁ on day 1. Solutions for nebulisation were prepared immediately before use from stock solutions of

ipratropium bromide 0.25 mg/ml without preservatives, salbutamol sulphate 5 mg/ml, and a 0.9% sodium chloride solution. The solutions were isotonic and the pH was 3.5. Drugs were nebulised by a HICO-Ultrasonic nebuliser type 806E (Hirtz, Cologne, Germany) with an output of 0.6 ml/min (3 ml during five minutes of tidal breathing). Patients wore a noseclip during nebulisation. Nebulised doses were 0.19, 0.38, 0.75, 1.5, and 3.0 mg ipratropium and 0.94, 1.88, 3.75, 7.5, and 15.0 mg salbutamol. The combination (ipratropium/salbutamol) was given in doses of 0.09/0.47, 0.19/0.94, 0.38/1.88, 0.75/3.75, and 1.5/7.5 mg. Subjects rested one hour after each inhalation before FEV₁ was measured again. The experiment was discontinued when FEV₁ increased less than 5% compared with the previous measurement. One hour after the final nebulisation a histamine challenge was performed.

DATA ANALYSIS

PC₂₀ values were log₂ transformed for analysis; change in PC₂₀ was measured in doubling concentrations. FEV₁ was expressed as a percentage of the predicted value (% predicted).¹⁴

Multivariate analysis of variance of repeated measurements was used for initial analysis. Dependent variables were FEV₁ and PC₂₀, and explanatory factors were treatment, bronchodilator administered, and two way interactions between treatment and bronchodilator administered. Student's *t* tests for paired observations were used to compare treatment regimens and bronchodilators when significant treatment and bronchodilator effects emerged. Trends and carry over effects were tested by adding "period" factor and the interaction term "treatment \times period" to the models. These were omitted from the final models when not significant.

The effects of combining the corticosteroids and bronchodilators were assessed in two ways. Firstly, the two way interaction factor of all combinations of corticosteroids and bronchodilators was evaluated by multivariate analysis of variance, the null hypothesis being that the interactive effect is zero—that is, that the observed value for the combination of corticosteroids and bronchodilators is equal to the sum of their separate effects (an additive effect). A positive interactive effect indicates that the effect of the combination was larger than the sum of the separate effects (synergistic), whereas a negative interactive effect implies a smaller effect from the combination than would be expected from the sum of their separate effects (antagonistic). Secondly, we assessed whether the values after combination of corticosteroids and bronchodilator, whatever the nature of their interaction, differed from the values after bronchodilator following the placebo treatment period; values after bronchodilator following the three treatment periods were compared by paired *t* tests.

Individual responses to corticosteroids and bronchodilators were calculated by multiple linear regression by using models which included dummy variables for budesonide, pred-

Table 1 Characteristics of subjects on day of selection for study

Patient No	Age (years)	Sex	Smoking status	Eosinophil count ($\times 10^6/l$)	FEV ₁ (l)	FEV ₁ (% predicted)	FEV ₁ %VC (%)	PC ₂₀ histamine (mg/ml)	Maintenance treatment
1	59	M	Former	88	2.90	76.3	61.7	0.71	Inhaled corticosteroids, ipratropium
2	64	M	Current	154	1.75	52.0	50.0	0.56	Inhaled corticosteroids, ipratropium, theophylline
3	49	M	Current	77	1.80	51.6	52.9	0.23	Inhaled corticosteroids, ipratropium
4	62	M	Current	429	1.50	44.5	39.0	0.14	Inhaled corticosteroids, ipratropium, theophylline
5	57	F	Current	99	1.45	58.2	58.0	0.75	Inhaled corticosteroids, ipratropium
6	58	M	Former	33	2.00	57.5	56.3	1.38	Inhaled corticosteroids, ipratropium
7	66	M	Current	33	1.85	70.9	40.2	0.30	Theophylline, promethazine
8	55	M	Former	<11	1.85	53.2	52.1	0.42	Promethazine
9	52	M	Current	<11	1.50	45.3	46.3	0.38	Inhaled corticosteroids, ipratropium
10	49	F	Former	22	2.00	79.1	72.1	2.33	Salbutamol

nisone, salbutamol, ipratropium, and two way interactions between these factors. A p value less than 0.05 was considered significant. Only p values less than 0.1 are mentioned in the text. All calculations were performed with the statistical software package SPSS/PC+, V3.1 (SPSS, Chicago, United States).

Results

Table 1 shows the clinical characteristics of the patients at randomisation. Two patients were excluded from the analysis because they developed an exacerbation: patient 9 dropped out during the first (prednisone) period and patient 10 during the second (budesonide) period. The analysis is based on the remaining eight patients. Order and carry over effects were not significant.

EFFECTS OF BRONCHODILATORS

All subjects received three doses of bronchodilator on each bronchodilator study day. The absolute increment in FEV₁ from step 2 to step 3 was always ≤ 0.10 (mean 0.03) litre for ipratropium and always ≤ 0.15 (mean 0.04) litre for salbutamol. Both bronchodilators individually and the combination caused significant changes in FEV₁ and PC₂₀ ($p < 0.001$, for both variables).

Dose-response curves of FEV₁ after the placebo period showed no substantial differences between the three bronchodilator curves (figure 1). Final FEV₁ values (table 2) were significantly higher after the inhaled bronchodilators than after placebo ($p = 0.004$ for ipratropium, $p = 0.008$ for salbutamol, and $p = 0.002$ for the combination). No significant differences existed between the two bronchodilators or between the combination of ipratropium and salbutamol and either drug alone. Individual responses varied within the group, though most subjects showed a somewhat larger response to salbutamol than to ipratropium (figure 2).

The effects of bronchodilators on histamine

responsiveness after the placebo period were less uniform (table 2). PC₂₀ values were significantly higher after salbutamol alone and the bronchodilator combination than after placebo, by 1.64 and 2.02 doubling concentrations ($p = 0.002$ and $p = 0.003$, respectively). The difference between ipratropium and placebo (0.83 doubling concentrations) was not significant. The PC₂₀ after salbutamol was significantly higher than that after ipratropium ($p = 0.02$). The effects of the combined salbutamol and ipratropium did not differ from that of salbutamol alone, and the difference from the effect of ipratropium alone (1.19 doubling concentrations) was not significant (p

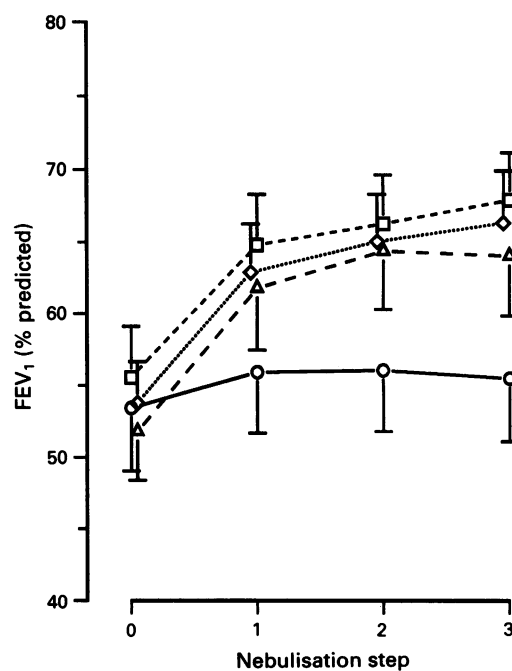


Figure 1 Effect of bronchodilators on FEV₁ after placebo treatment: placebo (○), ipratropium (△), salbutamol (◇), and combination of ipratropium and salbutamol (□). Differences between bronchodilators in terms of the final FEV₁ were not significant.

Table 2 Effects of corticosteroids and bronchodilators on FEV₁ and PC₂₀ histamine*

Treatment	Bronchodilator:			
	Placebo	Ipratropium	Salbutamol	Combination
	Mean (SE) FEV ₁ (% predicted)			
Placebo	55.5 (4.4)	64.0 (4.2)	67.9 (3.3)	66.3 (3.6)
Budesonide	55.2 (4.1)	64.7 (3.8)	68.5 (3.5)	66.1 (3.8)
Prednisone	58.9 (3.2)	68.8 (3.9)	70.2 (3.7)	70.2 (3.9)
	Log ₂ PC ₂₀ (mg/ml)			
Placebo:				
Mean (SE)	-0.87 (0.64)	-0.04 (0.55)	0.77 (0.56)	1.15 (0.63)
Geometric mean	0.55	0.97	1.71	2.22
Budesonide:				
Mean (SE)	-0.74 (0.66)	-0.01 (0.45)	1.63 (0.39)	1.54 (0.56)
Geometric mean	0.60	0.99	3.10	2.91
Prednisone:				
Mean (SE)	-1.09 (0.82)	0.30 (0.52)	1.44 (0.53)	1.80 (0.64)
Geometric mean	0.47	1.23	2.71	3.48

*Values measured after the final inhalation of bronchodilator.

= 0.10). Most subjects showed a larger change in PC₂₀ after salbutamol than after ipratropium (figure 2).

EFFECTS OF CORTICOSTEROIDS

Neither inhaled nor oral corticosteroids caused any significant change in FEV₁ or PC₂₀ (table 2). There was some variation within the group (figure 2).

COMBINED EFFECTS OF CORTICOSTEROIDS AND BRONCHODILATORS

The combined effects of corticosteroids and bronchodilators on FEV₁ and PC₂₀ were not significantly different from the sum of the separate effects for any combination. The shape and position of the FEV₁ dose-response curves for salbutamol after the placebo, budesonide, and prednisone periods did not differ (figure 3). The FEV₁ after the last dose of salbutamol did not differ significantly between prednisone and placebo ($p = 0.07$) or between budesonide and placebo or prednisone (table 2). The dose-response curves for ipratropium after placebo, budesonide, and prednisone are also shown in figure 3. Although mean FEV₁ values were higher after prednisone, the final FEV₁ values after ipratropium did not differ between the three periods.

PC₂₀ values after salbutamol were higher following corticosteroid treatment, by 0.86 doubling concentrations after budesonide and by 0.67 doubling concentrations after prednisone, compared with the placebo treatment (table 2). The PC₂₀ after ipratropium showed a small increase, of 0.03 doubling concentrations following budesonide and 0.34 doubling concentrations after prednisone, compared with placebo. None of these changes in PC₂₀ was significant.

Discussion

This study was carried out to investigate the effects of short term treatment with corticosteroids on the airway response to bronchodilators. High doses of inhaled or oral corticosteroids did not modify the effects of

salbutamol and ipratropium on FEV₁ and PC₂₀ in non-allergic subjects with chronic obstructive lung disease.

Conflicting results have been obtained in trials which attempted to estimate corticosteroid sensitivity in patients with chronic obstructive lung disease.^{4-9 16 17} A rapid response to oral corticosteroids, occurring one to four weeks after starting treatment, has been seen in patients with atopy, as well as a good

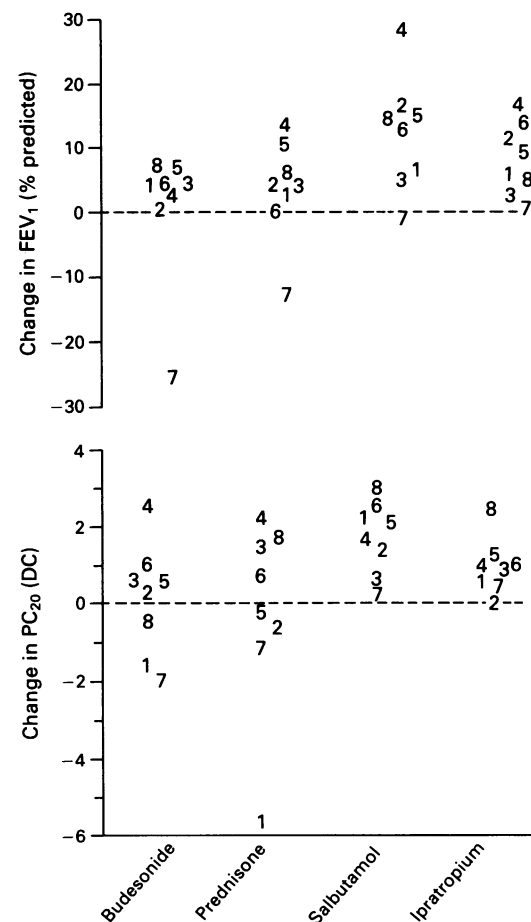


Figure 2 Individual changes in FEV₁ and PC₂₀ histamine after budesonide, prednisone, salbutamol, and ipratropium, compared with placebo (from multiple regression).

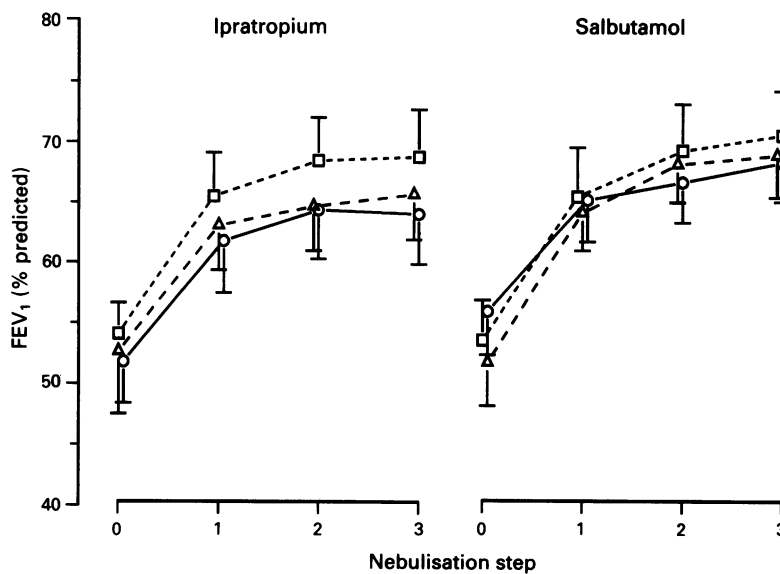


Figure 3 Effects of pretreatment with placebo (O), budesonide (Δ), and prednisone (\square) on ipratropium and salbutamol dose-response curves. No significant differences in final FEV_1 existed between treatments.

response to bronchodilators.⁴⁻⁶ We carefully excluded patients with asthma and atopy and found no effect with a short period of treatment with high doses of corticosteroids, though the responses varied within the group. The corticosteroid responses of subjects 1 and 7 after budesonide and prednisone were surprising as confounding factors such as pulmonary infections and seasonal influences were absent. Exclusion of these data changed mean values slightly but did not alter the outcome of statistical analyses.

Weir *et al* found that FEV_1 continued to increase after 14 days of corticosteroid treatment in some subjects with chronic airflow limitation¹⁸ and raised questions about the use of a two week prednisone regimen.¹⁹ Such a regimen is commonly used, and we chose it for our study. Weir *et al* included patients with high IgE concentrations and eosinophil counts, which makes comparison with our non-allergic group difficult.¹⁸ Subgroups of patients with chronic obstructive lung disease may differ with regard to required dose and formulation of corticosteroid treatment and in response time. More research needs to be directed at distinguishing these subgroups to enable prediction of corticosteroid sensitivity.

Patients with chronic obstructive lung disease generally respond better, or at least equally well, to an anticholinergic drug than to a β agonist in commonly used doses.²⁰⁻²³ Whether these doses are sufficient for a maximal effect is uncertain, especially as it has been suggested that responsiveness to β agonists decreases with age.²¹ We assessed cumulative dose-response curves, which show a greater airway response than non-cumulative and single dose studies,²⁴ and found a clear plateau with ipratropium; the plateau was less obvious with salbutamol. Airflow limitation in patients with chronic obstructive lung disease is determined by two components: a fixed part caused by damage of airway structure, and a reversible part, mainly caused by parasympathetic tone in airway

smooth muscle (other factors such as allergic processes contribute little). Salbutamol and ipratropium produce similar bronchodilation, which implies that they act equally strongly in counteracting this parasympathetic tone.

The mechanisms underlying the protection against constricting stimuli by bronchodilators are not completely understood.²⁵ β Agonists provide better protection against histamine than anticholinergics in patients with asthma²⁶⁻²⁹ and chronic bronchitis,²⁹ and the effect of β agonists, but not of anticholinergics, is dose dependent.²⁸ Bronchodilators may exert a protective effect by increasing airway diameter, since airway diameter is assumed to be a determining factor of responsiveness in patients with chronic obstructive lung disease.^{30,31} We found that salbutamol and ipratropium produced comparable values of FEV_1 , yet better protection by salbutamol was evident. This stronger functional antagonistic action of β agonists is probably mainly due to effects on smooth muscle cells but may also be mediated by reducing the histamine induced swelling of the airway wall. Cholinergic mechanisms—for example, vagal reflex mechanisms—do not seem to play an important part in the histamine induced obstruction.

In our study the effects of the combination of salbutamol and ipratropium were similar to the effects of salbutamol alone. However, we gave high nebulised doses of bronchodilator. Commonly used doses may show additive effects³² and produce fewer side effects, and may therefore be useful in clinical practice.

We did not find significant modifying effects of corticosteroids on bronchodilator action, but only a small group of patients was studied for a relatively short time. Generalisation of the results to the whole population of patients with chronic obstructive lung disease is therefore not unjustified. Nevertheless, some of the trends we observed are interesting and need further study. The higher PC_{20} values after salbutamol following treatment with budesonide and prednisone, and the raised dose-response curve for ipratropium after prednisone, both in the absence of corticosteroid effects on baseline values, were not significant but may be due to some synergistic effect. There is some evidence in the literature of an effect of corticosteroids on β agonist response. Corticosteroids are capable of restoring β responsiveness in previously non-responsive asthmatic patients¹⁰ and in normal subjects.¹² A synergistic effect of corticosteroids and β agonists in subjects without evidence of a diminished β responsiveness could not be shown.^{33,34} Studies *in vitro* have shown an increase in concentrations of β receptors after corticosteroid treatment.^{35,36} Future research, especially on the long term effects of corticosteroids on bronchodilator action, is needed.

In conclusion, our study showed that cumulative doses of nebulised salbutamol and ipratropium result in similar bronchodilatation in non-allergic subjects with chronic obstructive lung disease. Salbutamol, however, gave better protection against histamine challenge and may be preferable for clinical purposes.

Short term treatment with corticosteroids had no effects on airflow limitation and airway responsiveness and did not modify the bronchodilating and protective effects of bronchodilators.

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