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Chronic treatment with indacaterol and airway response to salbutamol in stable COPD

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Summary
Tolerance to both the bronchoprotective effect, and, to a lesser extent, the bronchodilator activity, occurs with all inhaled β_2-agonists. Assumed the importance of this topic and the lack of a clinical evaluation specifically designed to assess the impact of chronic administration of indacaterol on the response to salbutamol, we sought to compare the effect of 4-week treatment with indacaterol 150 μg once-daily versus formoterol 12 μg twice-daily on the dose-response curve to inhaled salbutamol (total cumulative dose of 800 μg) in a non-double-blinded, crossover, randomised, and controlled pilot trial that enrolled 20 outpatients with moderate to severe COPD. At the end of 4-week treatments, there was not a statistically significant difference between the two trough FEV_1 ($p = 0.16$), and both indacaterol and formoterol were able to produce a significant ($p < 0.001$) increase in FEV_1 mean differences (L) = indacaterol 0.15 (95% confidence interval (CI) 0.12–0.18); formoterol 0.10, (95% CI 0.08–0.12) 2 h after their inhalation. Salbutamol elicited an evident dose-dependent increase in FEV_1 and this occurred also after regular treatment with indacaterol and formoterol with a further mean maximum increase of 0.10L (95% CI 0.05–0.14) and 0.05L (95% CI 0.02–0.08), respectively. The differences between indacaterol and formoterol in FEV_1 increases after salbutamol were never statistically significant. The results of

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this study support the use of salbutamol as rescue medication for rapid relief of bronchospasm in patients suffering from COPD, even when they are under regular treatment with indacaterol.

Introduction

Tolerance to both the bronchoprotective effect, and, to a lesser extent, the bronchodilator activity, occurs with all β_2-agonists.[1] Bronchodilator tolerance develops rapidly, with a reduced response to salbutamol after a single dose of formoterol and reaches a plateau after 1 week of regular therapy.[2] Apparently, the degree of β_2-agonist tolerance increases with the degree of bronchoconstriction.[3]

Clinically relevant tolerance to rescue β_2-agonist treatment is likely to occur in asthmatic patients treated with LABAs.[4] Tolerance to the bronchodilator effects of LABAs may occur with their prolonged use also in COPD.[5] However in COPD, a pre-treatment with a conventional dose of formoterol or salmeterol does not prevent the possibility of inducing a further bronchodilation with salbutamol.[6] Moreover, the results of another study suggest that during chronic therapy with conventional doses of formoterol in moderate-to-severe COPD, the add on use of salbutamol does not improve peak expiratory flow and FEV_1 markedly, but is still effective in reducing air trapping, as shown by the increase in FVC and possibly dynamic pulmonary hyperinflation in the presence of tidal expiratory flow limitation at rest.[7]

The lack of induction of tolerance is an occurrence extremely useful because the usual approach in a COPD patient who complains of worsening dyspnoea and in which the physician suspects an increase of bronchial obstruction is to use salbutamol as rescue medication to produce rapid relief of bronchospasm.

Nonetheless, there are some differences between LABAs that could cause difference in airway response to salbutamol. Thus, high-efficacy agonists may cause a greater loss of receptors,[8] and it has also been suggested that relevant tolerance to rescue salbutamol treatment could be more likely with β_2-agonists that are able of a really long residency at the β_2-adrenoceptor.[9] This is because of prolonged, 24-h receptor occupancy and the associated propensity for agonist-promoted reduction in the number and coupling efficiency of β_2-adrenoceptors on airway smooth muscle and inflammatory cells, where such receptors are expressed.[9]

However, Battram et al.[10] evaluated the ability of indacaterol, which is the first LABA able to induce 24-h bronchodilation, formoterol and salmeterol to induce tachyphylaxis in guinea pigs. None of the compounds was subject to desensitization at any of the doses tested. Indeed, for indacaterol and formoterol, the inhibitory effect of each dose after 5-day treatment compared with that of a single treatment was enhanced and reached significance for the indacaterol dose of 0.006 and 0.6 μg/kg and for the formoterol dose of 0.0006 μg/kg. Such a phenomenon was not observed for salmeterol.

Assumed the importance of this topic and the lack of a clinical evaluation specifically designed to assess the impact of chronic administration of indacaterol on the response to salbutamol, we assessed whether a regular treatment with this once-daily LABA might modify the dose-response curve to inhaled salbutamol in patients with stable COPD.

Patients and methods

We studied 20 outpatients with moderate to severe COPD, They were ≥60 years of age, current or former smokers (>10 pack-years), reporting chronic cough with or without sputum production and/or dyspnoea when walking quietly on level ground. In addition, all patients had FEV_1 ≤70% of predicted normal, and a best post-bronchodilator (salbutamol 200 μg) FEV_1/FVC of less than 0.7. Table 1 describes the baseline characteristics of the randomised patients.

Patients had experienced no change in symptom severity or treatment in the preceding 2 months, had shown no signs of a respiratory tract infection in the month preceding or during the trial, and had not taken oral corticosteroids, other inhaled or oral bronchodilators, leukotriene modifiers or β_2-blockers for at least 2 months. Patients were allowed to continue taking inhaled corticosteroids, provided a regimen of regular use had been stable for at least 1 month previously. Patients with a history of allergic diseases such as allergic rhinitis, asthma and atopic dermatitis (eczema), and positive skin test or with a total blood eosinophil count >400 mm^{-3} were excluded. Patients were also excluded if they had any coexisting cardiovascular or lung disorder, a resting PaO_2 of less than 60 mm Hg, or use of long-term oxygen therapy (Fig. 1). Patients were asked to refrain from consumption of cola drinks, coffee, tea, and from smoking, in the 12 h before and also during the investigation.

The study was conducted according to the rules of the declaration of Helsinki and each patient gave written informed consent to all procedures.

This was a non-double-blinded, crossover, randomised, and controlled pilot trial. The total study duration was 10 weeks. It had three parts. Part 1 was the run-in period of 1-week duration that followed screening visit 1. During this period, patients received inhaled salbutamol for relief therapy and they were asked to withhold rescue salbutamol for 8 h prior to come to our outpatient office for the next visit at the end of the run-in period when baseline measurements (FEV_1 and FVC) were performed, and the eligibility of screened patients to participate in the randomized treatment periods was assessed. In addition to the qualifying spirometric tests, each patient was subjected to the evaluation of the response of his/her airways to increasing

Table 1 The baseline characteristics of the randomised patients.

Patients	Age	Gender	Race	Height (cm)	Weight (kg)	BMI	FEV_1 (% predicted)	FVC (% predicted)	Reversibility (% baseline)	Concomitant medications
Patients who received first indacaterol followed by formoterol										
1	73	M	Caucasian	175	90	29	66.6	84.0	12.2	
2	63	M	Caucasian	162	82	31	69.8	86.3	8.6	
3	65	M	Caucasian	170	82	28	39.8	60.4	13.7	Budesonide
4	64	M	Caucasian	170	58	20	31.1	58.0	7.6	Budesonide
5	65	M	Caucasian	170	78	27	40.3	61.2	9.3	Budesonide
6	73	M	Caucasian	174	88	29	67.9	83.3	5.2	
7	70	M	Caucasian	160	75	29	69.5	87.8	8.7	
8	76	M	Caucasian	161	87	34	30.5	57.1	8.8	Budesonide
9	64	F	Caucasian	155	58	24	68.6	88.7	17.6	
10	69	M	Caucasian	169	82	29	46.8	68.4	12.3	Budesonide
Patients who received first formoterol followed by indacaterol										
1	80	M	Caucasian	176	85	27	36.8	74.5	17.1	Budesonide
2	72	M	Caucasian	175	69	23	43.0	63.8	13.6	Budesonide
3	73	M	Caucasian	162	77	29	68.9	91.8	14.8	
4	63	M	Caucasian	163	84	32	68.4	88.4	9.2	
5	70	M	Caucasian	169	57	20	32.7	66.8	12.2	Budesonide
6	63	F	Caucasian	162	59	22	45.9	81.1	19.6	Budesonide
7	77	M	Caucasian	165	75	28	63.3	82.2	9.3	
8	68	M	Caucasian	175	81	26	42.0	59.5	18.9	Budesonide
9	64	M	Caucasian	170	86	30	52.4	71.6	13.3	
10	71	M	Caucasian	163	81	30	64.2	84.9	15.4	

dose of salbutamol. A dose-response curve to inhaled salbutamol was constructed 2 h after inhalation of placebo using a dose of 100, 100, 200 and 400 μg — that is a total cumulative dose of 800 μg. Dose increments were given at 20 min intervals with measurements being made 15 min after each dose.

Part 2 and part 3 constituted the randomized treatment periods. Each period was of 4-weeks' duration. At the end of the run-in period, at visit 2, eligible patients were randomized to one of the two open-label treatment sequences: (1) indacaterol 150 μg once-daily in part 2, formoterol 12 μg twice-daily in part 3; and (2) formoterol

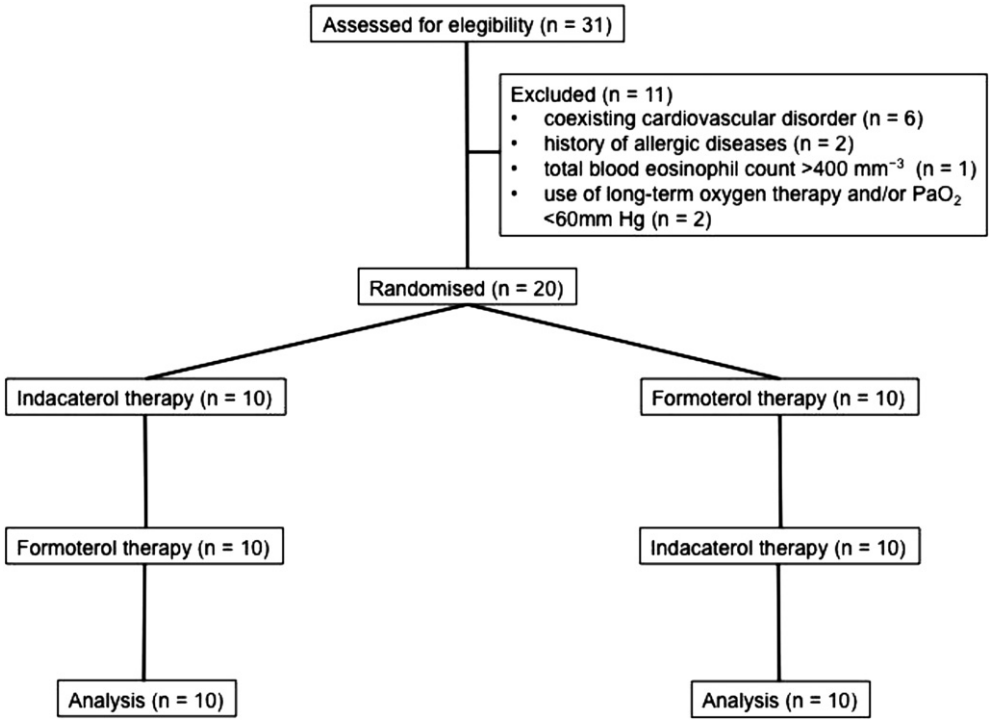

Figure 1 Consort diagram showing the flow of participants through each stage of the trial.

12 μg twice-daily in part 2, indacaterol 150 μg once-daily in part 3. At the end of each 4-week treatment, at 24 h after the last dose of indacaterol or 12 h after the last dose of formoterol, patients returned to our outpatient office and underwent spirometry for the assessment of trough FEV_1 and FVC and soon after they inhaled a further dose of indacaterol or formoterol. Two hours after the inhalation of each treatment, all patients underwent a new spirometry, and then a dose-response curve to inhaled salbutamol was constructed again. There was 1-week washout period between treatment periods during which the only medication allowed was salbutamol for relief therapy and, again, patients were asked to withhold rescue salbutamol for 8 h prior to come to our outpatient office for the next visit.

All experiments began at 9 a.m. to avoid well-known interference of the circadian rhythm on bronchomotor tone.

The maximum FEV_1 value during the dose-response curve to salbutamol was chosen as the primary outcome variable to compare the two treatments. Analysis of spirometric data for each treatment was performed using the Student's *t*-test for paired variables. Mean responses were also compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between the two treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits was used to identify where differences were significant. A probability level of $p < 0.05$ was considered as being of significance for all tests.

Results

All patients completed the study that lasted 10 weeks. Baseline FEV_1 values were not significantly different following each of the three treatment periods ($p > 0.05$).

At the end of 4-week treatments, there was not a statistically significant difference between the two trough FEV_1 ($p = 0.16$), and both indacaterol and formoterol were able to produce a significant ($p < 0.001$) increase in FEV_1 (mean differences (*L*) = indacaterol 0.15, 95% confidence interval (CI) 0.12—0.18; formoterol 0.10, 95% CI 0.08—0.12) 2 h after their inhalation (Fig. 2A).

Salbutamol induced a further dose-dependent increase in FEV_1 after both indacaterol and formoterol, but the increase after indacaterol was larger than after formoterol, at least with the two higher cumulative doses of salbutamol (salbutamol 400 μg: mean difference (*L*) = indacaterol 0.07, 95% CI 0.02—0.12; formoterol 0.03, 95% CI 0.007—0.05; and salbutamol 800 μg: mean difference (*L*) = indacaterol 0.10, 95% CI 0.05—0.14; formoterol 0.05, 95% CI 0.02—0.08), although differences between indacaterol and formoterol in FEV_1 increases after salbutamol were never statistically significant ($p = 0.083$, $p = 0.821$, $p = 0.121$ and $p = 0.073$, after 100, 200, 400 and 800 μg cumulative dose, respectively) (Fig. 2A). The FEV_1 area under the salbutamol response curve was lower after formoterol (0.18*L*; 95% CI 0.14—0.23) therapy compared to indacaterol (0.24*L*, 95% CI 0.14—0.34), although the difference was not statistically significant ($p = 0.271$).

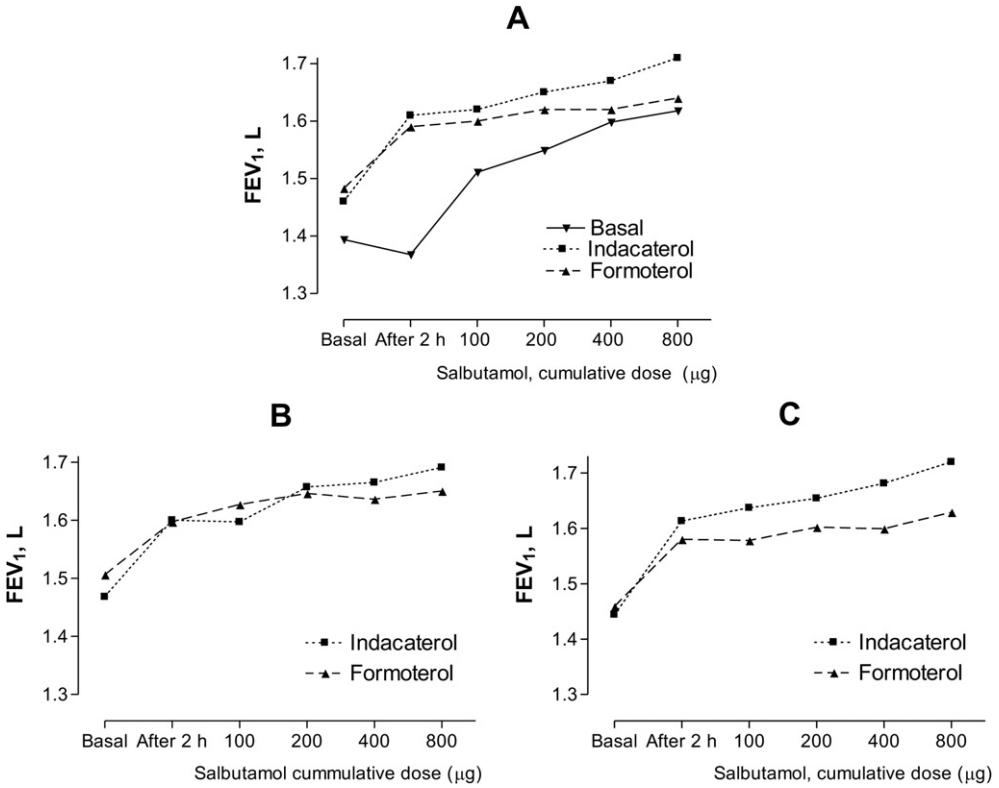

Figure 2 Mean dose-response curves to inhaled salbutamol construction at basal 2 h after inhaling placebo, and at the end of 4-week treatments 2 h after inhaling indacaterol, or formoterol, for FEV_1. A, all patients; B, patients who received first indacaterol followed by formoterol; C, patients who received first formoterol followed by indacaterol.

In the patients who received first indacaterol followed by formoterol, the mean increase caused by indacaterol was 0.13*L* (95% CI 0.08—0.18) and that elicited by formoterol was 0.09*L* (95% CI0.05—0.14), whereas in the patients who received first formoterol followed by indacaterol, it was 0.17*L* (95% CI 0.14—0,20) for indacaterol and 0.11*L* (95% CI 0.08—0.13) for formoterol, respectively (Fig. 2B and C). In the first group, the two higher cumulative doses of salbutamol induce a further mean increase in FEV_1 (salbutamol 400 μg: mean difference (*L*) = indacaterol 0.06, 95% CI 0.01—0.14; formoterol 0.04, 95% CI 0.001—0.08; and salbutamol 800 μg: mean difference (*L*) = indacaterol 0.09, 95% CI 0.02—0.16; formoterol 0.05, 95% CI 0.002—0.10) (Fig. 2B). Also, in the patients who received first formoterol followed by indacaterol, the two higher cumulative doses of salbutamol induce a further mean increase in FEV_1 (salbutamol 400 μg: mean difference (*L*) = indacaterol 0.07, 95% CI 0.02—0.15; formoterol 0.02, 95% CI 0.001—0.05; and salbutamol 800 μg: mean difference (*L*) = indacaterol 0.11, 95% CI 0.04—0.17; formoterol 0.05, 95% CI 0.003—0.10) (Fig. 2C).

Improvements in FVC closely reflected the FEV_1 results (Fig. 3).

Discussion

This study confirms that in COPD patients formoterol does not reduce the possibility of inducing a further bronchodilation with salbutamol[6] and, for the first time to the best of our knowledge, it shows that a regular treatment with indacaterol does not alter bronchodilator response to repeated doses of this short-acting β_2-agonist.

Our findings fit well with the documentation that on isolated human bronchi pre-contracted with 1 μM carbachol and at concentrations inducing ~20 and 35% inhibition, formoterol and indacaterol did not affect the potency of isoprenaline-induced bronchi relaxation.[11] Moreover, tolerance has not been observed with long-term indacaterol administration.[12—14] The lack of antagonism with short-acting β_2-agonists may have potential clinical connotations regarding the use of salbutamol as rescue therapy in common clinical practice.

Current knowledge does not allow us to establish whether the lack of tolerance is due to the pharmacological properties of β_2-agonists used in this study or the disease suffered by our patients.

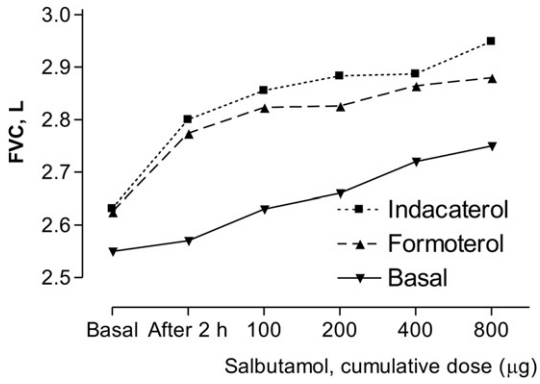

Figure 3 Mean dose-response curves to inhaled salbutamol construction at basal 2 h after inhaling placebo, and at the end of 4-week treatments 2 h after inhaling indacaterol, or formoterol, for FVC.

It still remains unclear whether functional tachyphylaxis is different in those who use different inhaled β-agonists, be they LABAs such as salmeterol, indacaterol, and formoterol, or short-acting β-agonists such as salbutamol.[15] In effect, we still do not know whether the degree of agonist-induced desensitization of the β_2-adrenoceptor is related to agonist efficacy (strength of signalling).

Charlton[8] has suggested that the maximal achievable response to the partial agonist reduces immediately upon loss of receptors, but the high-efficacy agonist can tolerate up to 90% loss of receptor before any effect is observed on the maximal response to the ligand. Hence, dose escalation with the high-efficacy agonist will result in a maintained response, even if 90% receptors are lost from the system. Increasing the dose of the low-efficacy agonist will not, however, gain any additional effect. Nevertheless, we must highlight that salmeterol, which is a low-efficacy agonist, has in cell-based studies exhibited resistance to agonist-induced β_2-adrenoceptor desensitization, raising the possibility that the intrinsic activity of an agonist may influence mechanisms of homologous desensitization.[16,17] Conversely, Düringer et al.[18] did not find evidence to support this conclusion. In particular, the reduced responsiveness did not correlate with high agonist intrinsic activity because the high-intrinsic-activity agonists isoprenaline and formoterol induced the least loss of responsiveness. In general, the lower-efficacy agonists caused a greater loss of responsiveness, likely because of the reduced wash out of the more lipophilic compounds, but there were exceptions to this pattern.[18] In particular, indacaterol induced much less desensitization than would be expected from its large degree of retention in the cells.[18] Individual agonists may induce specific receptor conformations to produce unique signalling patterns,[19—21] suggesting the possibility for each agonist to display a unique effect due to both receptor antagonism and desensitization.[18]

In any case, there has been some controversy in the literature regarding tolerance associated with long-term use of LABAs in patients with COPD.[22,23] Although tolerance to chronic administration of inhaled β_2-agonists has not been adequately addressed in patients with COPD, there seems to be much more tolerance to bronchodilators in asthma than in COPD. It is possible that, due to the different pathogenic mechanisms involved in bronchoconstriction in COPD compared to asthma, tolerance to β_2-agonists may not occur or the magnitude of tolerance may be different.[22] Tolerance is more noticeable with bronchoprotection than bronchodilation, perhaps reflecting the smaller number of β_2-adrenoceptors on inflammatory cells vs. the 40,000 β_2-adrenoceptors on human airway smooth-muscle cells.[24]

In conclusion, the results of this study support the use of salbutamol as rescue medication for rapid relief of bronchospasm in patients suffering from COPD, even if they are under regular treatment with indacaterol.

Conflict of interest statement

We declare that we have no conflict of interest with this study that has not been sponsored by any Drug Company.

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