Salmeterol and airway response to allergen

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BACKGROUND: Regular treatment with inhaled salbutamol (seven to 14 days) increases airway responsiveness to allergen.

OBJECTIVE: To assess the effect of salmeterol 50 µg twice daily for six days on the early asthmatic response to allergen (PC₁₅).

DESIGN: Double-blind, randomized, crossover trial comparing salmeterol with placebo (twice daily over six days) with one week or more washout. Forced expiratory volume in 1 s (FEV₁) and allergen PC₁₅ were measured 36 h after each treatment was discontinued.

SETTING: Tertiary care out-patient bronchoprovocation laboratory.

SUBJECTS: Fourteen atopic asthmatics well controlled with (n=5) or without (n=9) inhaled corticosteroids. Subjects did not use inhaled beta-agonists for at least two weeks before and during the trial.

RESULTS: FEV₁ was slightly but significantly lower 36 h after the last dose of salmeterol versus placebo (3.28±0.83 versus 3.40±0.88 L, P=0.032). Airway responsiveness to allergen increased by about half a doubling concentration (log₁₀ PC₁₅ 2.71±0.61 versus 2.85±0.61, P=0.047).

CONCLUSION: A six-day treatment course of salmeterol 50 µg twice daily resulted in a slight decline in FEV₁ and a modest increase in airway response to allergen at 36 h.

Key Words: Allergen, Airway response, Asthma, Inhaled corticosteroids, Salmeterol

Le salmétérol et la réponse des voies aériennes à un allergène

HISTORIQUE: La prise régulière de salbutamol en inhalation (7 à 14 jours) augmente la réactivité bronchique à un allergène.

OBJECTIF: Évaluer l'effet du salmétérol à raison de 50 µg deux fois par jour pendant six jours sur la réponse asthmatique précoce à la CP₁₅ d'un allergène.

MODÈLE: Essai à double insu, randomisé et croisé comparant le salmétérol et un placebo (deux fois par jour pendant six jours) avec une fenêtre thérapeutique d'une semaine et plus. Le volume expiratoire maximum/seconde (VEMS) et la CP₁₅ vis à vis d'un allergène ont été mesurés 36 heures après l'arrêt de chaque traitement.

CONTEXTE: Laboratoire de tests de provocation bronchique pour les patient externes dans un centre de soins tertiaires.

SUJETS: Quatorze patients souffrant d'asthme atopique bien maîtrisé avec (n=5) ou sans (n=9) corticostéroïdes en inhalation. Les sujets n'ont pas utilisés de β₂-agonistes pendant deux semaines ou plus précédant l'essai et pendant l'essai.

RÉSULTATS: Le VEMS avait légèrement chuté mais de manière significative 36 heures après la prise de la dernière dose de salmétérol comparativement au placebo (3,28±0,83 contre 3,40±0,88 L, P=0,032). La réactivité bronchique à l'allergène avait augmenté environ d'une moitié de doublement de la concentration (log₁₀ CP₁₅ 2,71±0,61 contre 2,85±0,61, P=0,047).

CONCLUSION: Un traitement de 6 jours avec du salmétérol à raison de 50 µg deux fois par jour a entraîné une légère chute du VEMS et une augmentation modérée de la réponse des voies aériennes à un allergène 36 heures après l'administration de la dernière dose.

When conventional inhaled beta-agonists are used regularly, partial tolerance rapidly develops to the bronchoprotective effect of these agents (1-3). It has also been demonstrated that seven to 14 days of salbutamol 800 µg/day by inhalation increases both the early and late responses to

inhaled allergen (3-5). Tolerance to the bronchoprotective effect of salmeterol is more pronounced than that seen with the short-acting beta-agonist (2), and occurs within 24 h of commencing the drug (6,7). The effect of salmeterol on airway response to allergen has not been addressed.

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PATIENTS AND METHODS

Subjects: Fourteen atopic asthmatic subjects were studied. Subjects were either patients in the Respiratory Clinic at the Royal University Hospital, Saskatchewan, Saskatchewan or volunteers (Table 1). The asthmatics were well controlled with (n=5) or without (n=9) inhaled corticosteroids. Subjects had not required inhaled beta-agonists for at least two weeks before the study and did not use them for the study's duration. Forced expiratory volume in 1 s (FEV₁) was 70% of predicted or greater, methacholine PC₂₀ (8) was 8 mg/mL or less, and all subjects were known to have an early asthmatic response to allergen challenge in the laboratory. Subjects had no allergen exposure or respiratory tract infections for four weeks before or during the study. The study was approved by the Ethics Committee at the University of Saskatchewan, and signed informed consent was obtained.

Allergen challenge tests: Allergen challenges were done as previously outlined (3-5). After a rest period to ensure stability, FEV₁ was measured in triplicate. Subjects then inhaled doubling concentrations of allergen for 2 mins of tidal breathing. Allergens were nebulized with a Wright nebulizer (Aerosol Ltd, Colchester, United Kingdom) calibrated to give an output of 0.13 mL/min (driving flow 7.5 to 9.5 L/min). The aerosols produced were passed into a Hans Rudolph valve (Hans Rudolph Inc, Missouri), and patients inhaled them through a mouthpiece. Two ventilator filters were placed on the expiratory side of the valve to capture the exhalate and uninhaled nebulizate, thus preventing allergen from entering the room air and minimizing exposure of both the subject and any other person in the laboratory to aerosolized allergen. FEV₁ was repeated in duplicate 10 mins after each inhalation; inhalations were continued until the 10 min FEV₁ had fallen 13% or greater. FEV₁ was then monitored every 10 mins until the maximum decrease in FEV₁ had been recorded, generally at 20 or 30 mins. Following the assessment of the early asthmatic response, a single dose of fluticasone (Flovent, Glaxo Canada) or beclomethasone dipropionate

(Becloforte, Glaxo Canada) 500 µg was administered by inhalation; this dose of inhaled corticosteroid is known to inhibit the late asthmatic response (9). The early asthmatic response was measured as an allergen PC₁₅ calculated by an algebraic formula from the noncumulative log dose versus response curve.

Study design: This study was a double-blind, randomized, crossover comparison of freon-propelled metered dose inhaled placebo two puffs twice daily for six days versus salmeterol 25 µg/puff two puffs twice daily for six days; there was a one week or longer washout. Subjects took their inhaler twice daily at approximately 12 h intervals. Subjects attended the laboratory 36 h after the last of the 12 doses of each drug, and spirometry followed by an allergen PC₁₅ was recorded. Subjects were supplied with ipratropium bromide 20 µg/puff (Atrovent, Boehringer Ingelheim) to use if rescue medication was required during the trial period so as to avoid the use of inhaled beta-agonists.

Analysis: Major end-point for analysis was the allergen PC₁₅ that was logarithmically transformed. A secondary end-point was the baseline FEV₁ before allergen challenge. Results were analyzed by a computerized two-way (subject, treatment) ANOVA (Statistix 4.1 Analytical Software, Tennessee).

RESULTS

The trial was completed by all 14 subjects without adverse event. Ipratropium bromide was not required by any subject. Four subjects could accurately identify the active treatment, eight perceived no difference and two guessed incorrectly. Four subjects (patients 2,3,6,10) felt somewhat worse asthma control while using salmeterol; two suspected this was placebo, while two suspected this was active because they felt 'different'. All four had a lower FEV₁ 36 h after salmeterol versus after placebo (Table 2).

The allergen PC₁₅ was significantly lower 36 h following discontinuation of salmeterol compared with the placebo.

TABLE 1
Anthropometric and challenge data

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	FEV ₁ (L)	Methacholine PC ₂₀ (g/mL)	Allergen	Inhaled corticosteroid (µg/day)
1	21	F	160	48	2.89	0.87	Horse	800 BUD
2	21	M	183	68	4.27	0.50	Weed	none
3	26	M	180	73	4.44	8.0	Birch	500 BDP
4	22	M	174	70	3.66	3.7	Grass	none
5	24	F	163	58	3.21	2.0	Weed	none
6	23	M	190	86	4.96	3.2	Cat	none
7	23	M	185	123	4.44	1.5	Grass	none
8	23	F	170	61	3.55	2.7	Birch	250 BDP
9	49	M	170	64	2.54	0.31	Grass	none
10	21	M	170	67	3.88	0.64	Cat	none
11	21	F	173	68	3.42	4.0	Horse	none
12	21	F	154	55	2.48	1.6	Grass	none
13	24	F	160	52	2.44	0.73	Rabbit	500 BDP
14	45	F	155	51	2.09	0.50	Horse	500 BDP

BDP Beclomethasone dipropionate; BUD Budesonide; F Female; FEV₁ Forced expiratory volume in 1 s; M Male

The log₁₀ PC₁₅ was 2.71±0.61 (geometric mean 512 protein nitrogen units [PNU]/mL) compared with 2.85±0.61 (geometric mean 708 PNU/mL), *P*=0.047 (Table 2). FEV₁ was also slightly but significantly lower following discontinuation of the salmeterol. FEV₁ was 3.28±0.83 L after salmeterol compared with 3.40±0.88 L following placebo, *P*=0.032 (Table 2). The number of patients (patients 1,3,8,13,14) using inhaled corticosteroid was too small to analyze separately; however, there was no obvious difference compared with those not on inhaled corticosteroid (Table 2).

DISCUSSION

These results show that 36 h after a six-day course of twice daily salmeterol, airway responsiveness to allergen assessed by the early asthmatic response was significantly greater. The difference was slightly less than a half a doubling concentration. FEV₁ was also significantly lower.

Our previous studies with salbutamol and the early asthmatic response have shown that a seven- to 14-day course of salbutamol 200 µg four times daily caused a fall in allergen PC₁₅ or PC₂₀ of between one-half and one doubling concentration (3-5). We are aware of only one publication that addresses the chronic use of salmeterol and allergen, an abstract by Giannini et al (10). This study assessed the bronchoprotective effect at 1 h after the first and last dose of salmeterol administered twice daily for a week. The first dose of salmeterol completely inhibited the early asthmatic response to allergen. At the end of one week, the last dose of salmeterol no longer provided any protection against the allergen-induced early asthmatic response.

Regular use of salmeterol produces a greater tolerance to the bronchoprotective effect of beta-agonist than does shorter-acting beta-agonists. Cheung et al (2) demonstrated that 50 µg of salmeterol initially shifted the methacholine PC₂₀ by 10-fold (3.3 doubling doses), whereas after weeks 4 and 8, the shift was reduced to twofold (one doubling dose) (2). By contrast, conventional beta-agonists produce a smaller degree of tolerance. Terbutaline used for one week caused a reduction in the terbutaline-induced methacholine dose-shift from 2.7 to 2.2 doubling doses (1), while salbutamol for two weeks caused a reduction from 3.2 to 2.6 doubling doses (3). This tolerance occurs within 24 h after starting salmeterol and results in a reduction in salbutamol-induced inhibition of methacholine (6,7). Salmeterol-induced tolerance to the bronchoprotective effect is particularly marked when studying indirect stimuli, such as exercise (11) and allergen (10). Salmeterol also produces lessened bronchodilator response to salbutamol and the reduction in non-pulmonary beta-agonist effects, such as tremor, hypokalemia and tachycardia (12). The clinical relevance of the loss of bronchoprotection is uncertain, particularly with reference to artificial stimuli, such as methacholine, adenosine monophosphate, etc. Natural stimuli (eg, exercise, allergen) are more clinically relevant, and there is greater loss of bronchoprotection against such stimuli when beta-agonists have been used regularly (3,10,11), particularly in the case of salmeterol (10,11).

TABLE 2
Results of baseline FEV₁ and allergen PC₁₅ after one week of placebo and one week of salmeterol

Patient	Log ₁₀ allergen PC ₁₅ (mg/mL)		FEV ₁ (L)	
	Placebo	Salmeterol	Placebo	Salmeterol
1	1.65	1.78	2.86	2.79
2	3.24	3.56	4.24	4.02
3	2.85	2.69	4.11	3.79
4	3.33	3.46	3.79	3.61
5	3.21	3.04	3.05	3.15
6	3.40	3.57	4.93	4.58
7	3.03	2.85	4.37	4.36
8	3.16	2.84	3.32	3.56
9	1.75	1.64	2.71	2.49
10	3.16	2.58	3.94	3.55
11	2.56	2.50	3.49	3.55
12	3.05	2.92	2.45	2.44
13	3.49	3.49	2.41	2.15
14	2.03	1.96	1.89	1.84
Mean	2.85	2.71	3.40	3.28
SD	0.61	0.61	0.88	0.873
Geometric mean	708	513		
P value	0.047		0.032	

FEV₁ Forced expiratory volume in 1 s

Because salmeterol produces greater loss of bronchoprotection than does salbutamol, we had anticipated that we might observe a greater increase in responsiveness to allergen. This seemed particularly likely because the allergen-induced early asthmatic response assessed 1 h after the last dose of salmeterol (twice daily for one week) in Giannini's study was not different from placebo. The increased response to allergen in the current study, slightly less than half a doubling concentration, is similar to, or slightly less than, that produced by salbutamol. In three studies, we have shown falls in allergen PC₁₅ or PC₂₀ ranging between 0.6 and 0.9 doubling concentrations after seven to 14 days salbutamol 800 µg/day (3-5). It is reassuring that the allergen effect produced by regular use of salmeterol is relatively small.

The mechanism of the increased airway response to allergen remains obscure. It appears to be a separate issue to the loss of protection of beta-agonists. In addition, increased allergen responsiveness requires a larger daily dose of beta-agonist than that associated with lessened bronchoprotection (5). It is attractive to speculate that, after regular use of beta-agonists, allergen exposure results in a greater (50% to 100%) release of mast cell mediators. Perhaps subsequent greater degrees of airway inflammation could explain the enhanced late response (4,13). Both increased mediators and increased inflammation are testable hypotheses and are being investigated (13). Allergen exposure (likely via allergen-induced airway inflammation) is important in the pathogenesis of asthma (14). We feel that the beta-agonist-induced increase in airway responsiveness to allergen is probably more important than tolerance to beta-agonist. Others share this view (15).

The extremely long duration of action of salmeterol made selecting a time of measurement difficult. The goal was to study allergen PC₁₅ as soon as reasonably possible outside the duration of salmeterol's pharmacological effect. We selected 36 h because this is the time interval used by others (3,12), and 36 h is 12 h beyond salmeterol's known 12 to 24 h duration of action.

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