



Salbutamol tolerance to bronchoprotection: course of onset

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ABSTRACT

Background: Regular use of inhaled β -agonist leads to tolerance to its bronchoprotective effect. This occurs within 12 hours with salmeterol and has been documented at 1 week for salbutamol. The course of onset after introduction of salbutamol has not been investigated.

Objective: To determine the course of onset of tolerance to the bronchoprotective effect of salbutamol against methacholine.

Methods: Thirteen individuals with mild asthma completed a randomized, double-blind, placebo-controlled, cross-over study. Each treatment period consisted of 7 twice-daily doses (2 puffs of 100 μ g of salbutamol or placebo). Methacholine challenges were conducted 24 hours apart on 4 consecutive days, 10 minutes after the first, third, fifth, and seventh doses. The 2 treatment periods were separated by at least 14 days.

Results: Methacholine provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC_{20}) values during the 4 days of placebo treatment did not significantly differ (analysis of variance $P = .79$). A single dose of salbutamol shifted the methacholine PC_{20} approximately 5-fold from a geometric mean of 2.1 mg/mL to a geometric mean of 10.7 mg/mL. Maximal bronchoprotection after the active treatment occurred on day 2 after the third dose, which was significantly higher than on day 1 after the first dose ($P = .04$). After the fifth dose the methacholine PC_{20} was trending downward, and on day 4 the bronchoprotective effect of salbutamol had significantly decreased from its peak protection ($P = .001$).

Conclusion: The detrimental effects on bronchoprotection after regular use of salbutamol manifest after 5 doses and are significantly reduced from peak protection after 7 doses.

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Introduction

Salbutamol (albuterol) is the most common short-acting β_2 -agonist used for symptom relief and prevention in asthma. These agents are currently recommended for as needed use only, with the required amount being used as a measure of asthma control; the guidelines recommend that inhaled β_2 -agonist should be required no more than 3 times a week.¹ Regular use of salbutamol results in tolerance to bronchoconstriction induced by methacholine.² Tolerance to the bronchoprotecting³ and bronchodilating⁴ effects of long-acting β -agonists occurs remarkably rapidly, after 1 or 2 doses.^{3–5} Twice daily administration of 200 μ g of salbutamol results in tolerance after 7 days.⁶ The rapidity of onset of this tolerance is not known. This study was designed to determine the course of the development of tolerance to the bronchoprotective effect of salbutamol against methacholine-induced bronchoconstriction during an 84-hour period.

Methods

We performed a double-blind, randomized, crossover study in 13 evaluable patients with mild asthma. The study was approved by the University of Saskatchewan Biomedical Research Ethics Board, and written consent was obtained.

Patients

Fifteen patients, ages 18 to 65 years, with a diagnosis of mild asthma were recruited from the University of Saskatchewan student body and from a pool of participants from previous studies in our laboratory. Patient criteria included producing a forced expiratory volume in 1 second (FEV_1) greater than 70% predicted, no significant medical comorbidities, and no infection, allergen exposure, or other exacerbation for more than 4 weeks before the study. Patients were required to refrain from β -agonist use for at least 2 weeks before the study. Inhaled glucocorticosteroid medication was allowed provided the dose had been stable for at least 4 weeks (2 patients). In addition, an emergency ipratropium bromide (Atrovent; Boehringer Ingelheim, Ingelheim, Germany) inhaler was provided to patients to be taken if they experienced symptomatic

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Table 1
Demographic characteristics of the study patients

Patient No.	Sex	Age, y	Height, in	Weight, lb	Baseline FEV ₁ , L	FEV ₁ , % predicted
SLS001	M	64	66	145	2.35	74
SLS002 ^a	M	22	77	211	6.50	120
SLS003	F	23	62	145	2.53	107
SLS004	M	22	67	145	3.39	78
SLS005	F	24	64	140	2.35	70
SLS006	F	25	63	135	3.05	74
SLS007	F	25	65	130	2.86	83
SLS008	M	26	66	145	2.93	71
SLS009	F	49	65	135	2.80	99
SLS010	F	22	62	130	3.71	114
SLS011	F	34	62	113	2.87	97
SLS012 ^a	F	32	67	133	3.30	97
SLS013	M	35	70	180	3.58	83
SLS014	F	25	67	205	3.42	98
SLS015	M	23	77	175	5.38	96

Abbreviation: FEV₁, forced expiratory volume in 1 second.

^aPatient's data were not included in the final analysis.

wheezing or discomfort associated with bronchoconstriction. Pregnant or lactating women were excluded from this study.

Study design

At the commencement of the study, patients were asked to fill out a demographic sheet that included parameters such as height, age, weight, last asthma exacerbation, last upper respiratory tract infection, any allergies, and exposure to allergies. Female patients were asked to take a urine pregnancy test on the first day of each treatment period. The 2 treatments used in this study were salbutamol sulphate (Ventolin HFA) at 100 µg per actuation (total of 200 µg per dose) and identical-appearing masked placebo. The researchers and patients were masked to the treatment used by each patient, and the order of treatment periods was randomized. Each treatment period consisted of treatment administrations for 3.5 days (7 doses). Doses 1, 3, 5, and 7 were taken at the same time each day in the laboratory, and doses 2, 4, and 6 were taken by the participants at home a mean (SD) of 12 (4) hours after the laboratory dose.

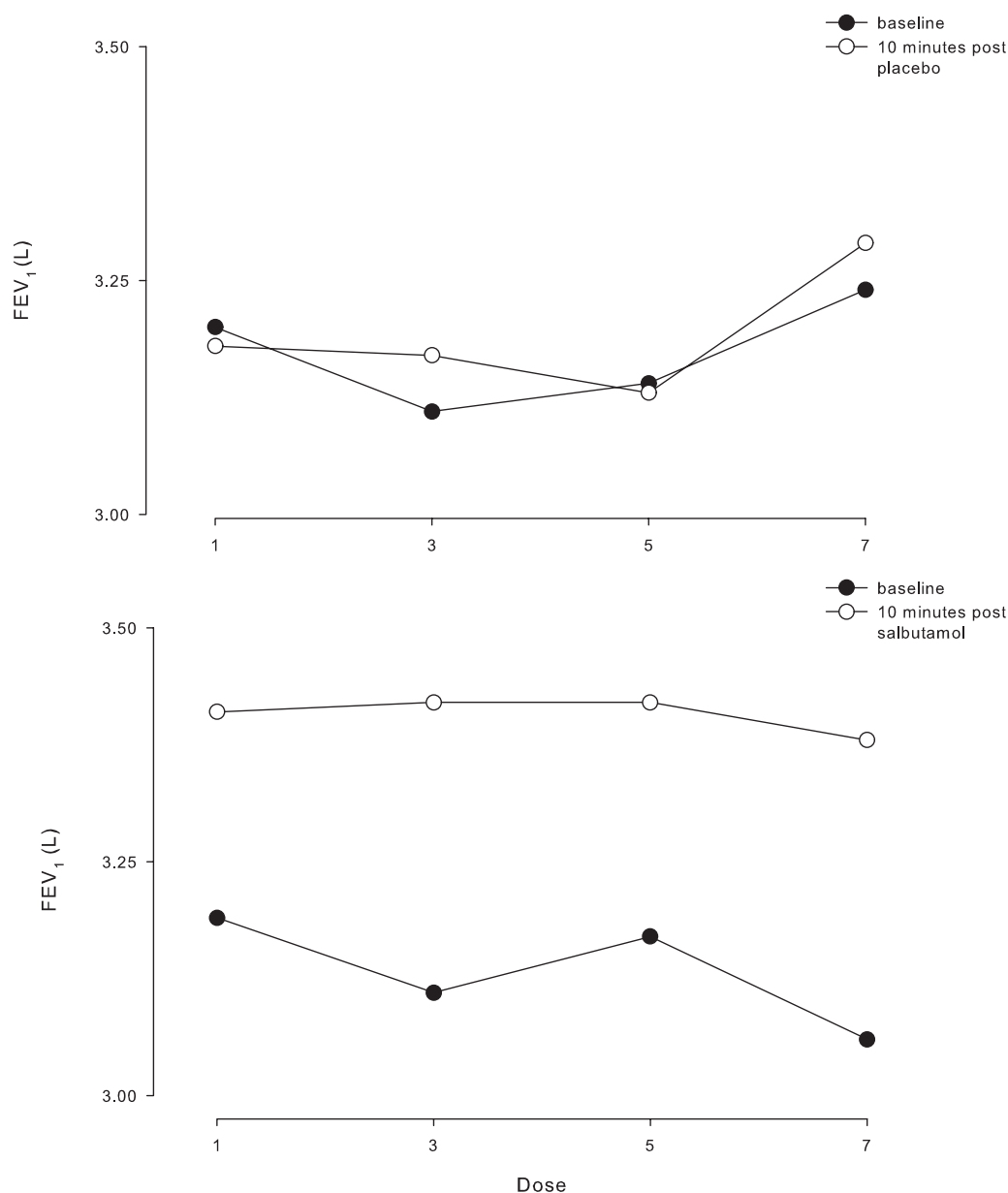


Fig. 1. Mean forced expiratory volume in 1 second (FEV₁) before (filled circles) and 10 minutes after (open circles) the 200-µg masked treatment.

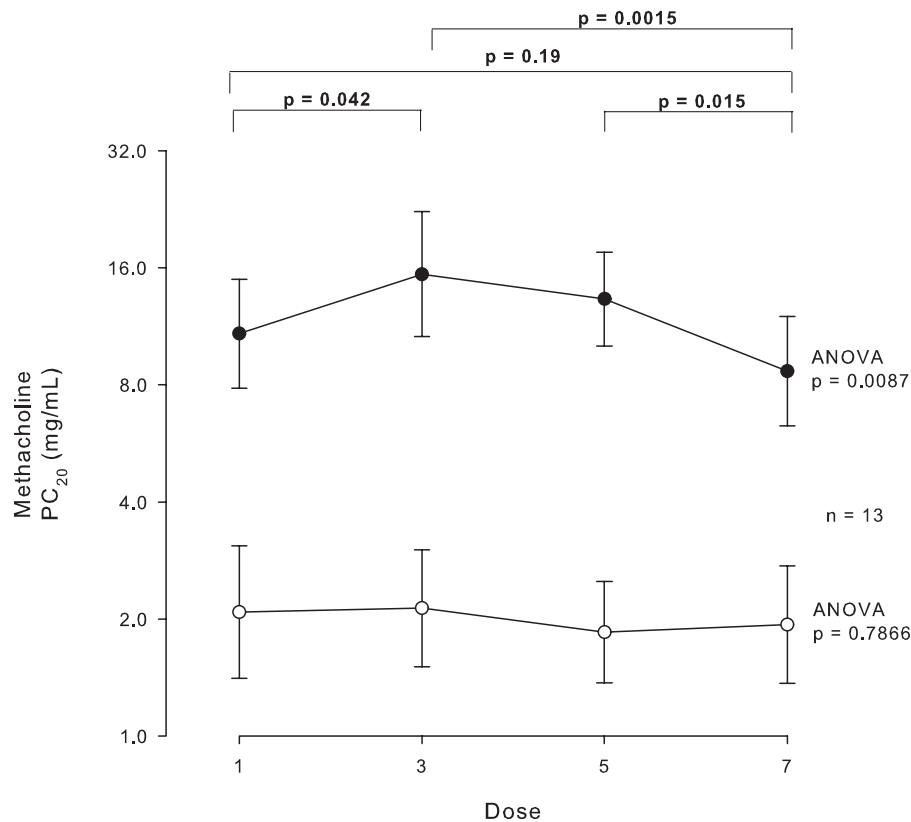


Fig. 2. Geometric mean methacholine provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC_{20}) values after the first, third, fifth, and seventh doses in the placebo (open circles) and salbutamol (closed circles) groups. ANOVA indicates analysis of variance.

Before doses 1, 3, 5, and 7 baseline lung function was measured to capture 3 reproducible (within 5% of each other) flow volume efforts. Patients were then coached on proper inhalation technique, the inhaler was actuated into the air twice, and the patients took 2 puffs of treatment from the masked aerosol inhaler. Ten minutes after the inhalation of the treatment, FEV_1 was measured in duplicate followed by administration of a methacholine challenge.

Methacholine challenge

The 2-minute tidal breathing methacholine challenge was performed according to the guidelines.⁷ Patients inhaled 0.9% sodium chloride (normal saline) for 2 minutes from a continuous output Bennett-Twin nebulizer calibrated to deliver 0.13 mL/min of aerosol. FEV_1 was measured again at 30 and 90 seconds after inhalation. This process was repeated using doubling concentrations of methacholine, starting at 0.25, 0.5, or 1.0 mg/mL, depending on the patient's medical history and baseline spirometry, and continuing until either a concentration of 256 mg/mL was reached or until the patient experienced a decrease in FEV_1 of 20% or more from the lowest postsaline FEV_1 . Percent decrease in FEV_1 was calculated from the lowest postsaline to the lowest postmethacholine value, and the provocation concentration of methacholine causing a 20% decrease in FEV_1 (PC_{20}) was calculated from the log concentration vs the response curve.⁸ If the decrease in FEV_1 was 17% to 19.9%, no further concentrations were given to avoid patient discomfort and the use of an emergency bronchodilator; the PC_{20} was extrapolated as previously documented.⁹

Statistical analysis

Methacholine PC_{20} values were log transformed for analysis. Methacholine PC_{20} data and FEV_1 data were both analyzed with a 2-way analysis of variance (patient and day). If appropriate, multi-

ple comparisons by least-squares difference of the means were performed. The computerized statistical program STATISTIX for Windows (Analytical Software, Tallahassee, Florida) was used.

Results

Of the 15 patients recruited for the study, 2 were not included in the final analysis, resulting in a total count of 13 participants. Patient demographic characteristics are given in Table 1, including those for patients 2 and 12, who were excluded from the final analysis because of insufficient responsiveness to the methacholine challenge and noncompletion of the study, respectively.

Mean FEV_1 data are presented in Figure 1. Placebo arm baseline FEV_1 values did not differ during the 4 treatment days (analysis of variance [ANOVA] $P = 0.6$). Mean baseline FEV_1 values during the active treatment period were 3.19, 3.11, 3.17, and 3.06 L for days 1, 2, 3, and 4 respectively (ANOVA $P = .04$). The day 4 values are significantly lower than the day 1 values ($P = .01$).

As depicted in Figure 2, no significant difference was found in methacholine PC_{20} between placebo days (geometric mean PC_{20} range, 1.8–2.1 mg/mL; $P = .79$). A single 200- μ g dose of salbutamol increased the methacholine PC_{20} from a geometric mean of 2.1 mg/mL to 10.7 mg/mL. Maximal bronchoprotection was reached on day 2; methacholine PC_{20} was significantly greater than on day 1 ($P = .04$). The PC_{20} was lower on day 4 compared with days 1, 2, and 3 ($P = .19$ [nonsignificant], .02, and .002, respectively; ANOVA $P = .009$).

Bronchodilation (Table 2) was not observed during placebo treatment (ANOVA $P = .13$). Mean percent bronchodilation values for the salbutamol treatment arm (10-minute postsalbutamol FEV_1 vs baseline FEV_1) were 7.0%, 9.4%, 7.8%, and 10.2% for days 1, 2, 3, and 4, respectively (ANOVA $P = .03$). The day 4 values were signif-

Table 2
Mean 10-minute posttreatment percent bronchodilation

Group	Day 1	Day 2	Day 3	Day 4	ANOVA P value
Placebo	−0.98	1.4	−0.26	1.0	.13
Salbutamol	7.0	9.4 ^a	7.8	10.2 ^b	.03

Abbreviation: ANOVA, analysis of variance.

^a $P < .05$ vs day 1.

^b $P < .05$ vs day 1 and day 3.

icantly greater than the day 1 and day 3 values; the day 2 values were significantly greater than the day 1 values ($P < .05$).

Discussion

A decrease in the bronchoprotective effects of salbutamol against methacholine begins after 5 doses (200 μ g per dose every 12 hours). The loss of bronchoprotection is significant after the seventh dose compared with the maximal bronchoprotection achieved after the third dose. On the basis of previously reported data for the long-acting β -agonist salmeterol (ie, 12 and 24 hours),^{3,5} we had anticipated a much quicker onset in the loss of bronchoprotection for the short-acting β -agonist salbutamol. Nonetheless, our data support a much earlier development of tolerance than the previously known timeline of 7 and 14 days.^{2,6}

We did not anticipate a significant increase in bronchoprotection (ie, higher methacholine PC₂₀) after the third dose of salbutamol compared with the first dose of salbutamol. This increase occurred in 6 of the 13 patients, and only 1 patient was more responsive to methacholine at this time point. Reasonable explanations include a lack of inhaler priming and poor inhalation technique; however, both of these were paid close attention. Admittedly, the use of a spacer device may have resulted in a different outcome; however, bronchodilator indicators, such as percent increase and absolute volume increase in FEV₁, are not consistently present in those whose methacholine PC₂₀ increased or absent in those whose methacholine PC₂₀ did not increase. We are not aware of any previously reported data describing methacholine PC₂₀ responses after the administration of clinically relevant doses of salbutamol. Loss of bronchoprotection after only 2 doses of salmeterol has been described, and we expected a similar pattern in the onset of tolerance to salbutamol as was found with salmeterol.

Another unexpected finding with active treatment was the significantly lower baseline FEV₁ on day 4 compared with day 1. Eleven of the 13 evaluable patients presented with lower (mean, 183 mL) FEV₁ values on day 4. Mean baseline FEV₁ data during

placebo treatment did not differ, and although not statistically significant, the highest FEV₁ occurred on day 4 during this treatment arm. Again, we are unaware of any deleterious effects on baseline airway tone after 3.5 days of salbutamol use. There are data to support a loss of bronchodilator action of short-acting β -agonists after regular use of long-acting β -agonists. In our study, the magnitude of bronchodilation during active treatment was greatest on day 4, and this was significantly different than day 1. The greater bronchodilatory effect is likely explained by the concomitant significantly lower baseline FEV₁ on day 4. The significance of the lower baseline FEV₁ and the increased bronchodilation on day 4 of the active treatment arm are therefore difficult to interpret.

In summary, the onset of tolerance to the maximal bronchoprotective effects of regular salbutamol use (200 μ g twice daily) against methacholine-induced bronchoconstriction occurs after 7 doses (ie, 3.5 days). The onset is delayed when compared with long-acting β -agonists but occurs sooner (from maximal bronchoprotection) when compared with previously reported salbutamol data. The onset is trending toward significance from baseline bronchoprotection and may occur earlier than the known timeframe of 7 days. Additional unexpected observations were that the maximal bronchoprotective effect was not present until after the third dose and that baseline lung function was significantly decreased after 4 days of regular salbutamol use. The clinical implications of our findings are, at this point, limited.

References

- [1] Loughheed MD, Lemiere CL, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J*. 2012;19:127–164.
- [2] Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet*. 1993;342:833–837.
- [3] Drotar DE, Davis EE, Cockcroft DW. Tolerance to the bronchoprotective effect of salmeterol 12 hours after starting twice daily treatment. *Ann Allergy Asthma Immunol*. 1998;80:31–34.
- [4] Haney S, Hancox RJ. Rapid onset of tolerance to beta-agonist bronchodilation. *Respir Med*. 2005;99:566–571.
- [5] Bhagat R, Kalra S, Swystun V, Cockcroft DW. Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest*. 1995;108:1235–1239.
- [6] Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airway responsiveness to allergen and reduced protection versus methacholine: dose response. *J Allergy Clin Immunol*. 1996;97:47–52.
- [7] Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med*. 2000;161:309–329.
- [8] Cockcroft DW, Murdock KY, Mink JT. Determination of histamine PC₂₀: comparison of linear and logarithmic interpolation. *Chest*. 1983;84:505–506.
- [9] Jokic R, Davis EE, Cockcroft DW. Methacholine PC₂₀ extrapolation. *Chest*. 1996;114:1796–1797.