

The effect of inhaled albuterol in moderate to severe asthma

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Background: Some recent clinical investigations suggest that regular use of inhaled bronchodilators may lead to deterioration in asthma control.

Objective: The purpose of this study was to evaluate the effect of albuterol dosing schedule on clinical outcome in subjects with moderate to severe stable asthma.

Methods: Seventeen adults were randomized to two 15-week treatment periods in a double-blind crossover design. Throughout the study, subjects were instructed to take two inhalations four times daily from an unlabeled "test" canister. In the four times daily and as-needed (QID+PRN) period, this canister contained albuterol; in the as-needed (PRN) period, it contained placebo. A "rescue" albuterol canister was available for as-needed use at all times. Inhaler actuations from both the test and rescue canisters were electronically recorded. Outcome measures included prednisone requirements, morning and evening symptoms and peak expiratory flow rates, total and nighttime rescue albuterol use, and asthma-specific quality of life.

Results: The two treatment periods did not differ in symptoms, nighttime albuterol use, or asthma quality of life. During the QID+PRN period both morning and evening peak expiratory flow rates were significantly higher ($p < 0.01$ and 0.001 , respectively) and total rescue use of albuterol was significantly less ($p < 0.05$) than the PRN period. Days on prednisone tended to be lower in the regular dosing period ($p = 0.08$).

Conclusion: In our sample of patients with moderate to severe asthma, four times daily dosing of albuterol did not lead to deterioration of asthma control. (*J Allergy Clin Immunol* 1996;98:295-301.)

Key words: Asthma, peak expiratory flow rate, albuterol, compliance, quality of life

Although inhaled β -adrenergic agonists are the most effective bronchodilators available for asthma, their regular use may lead to poorer control of symptoms. In what has become a classic investigation, Sears, Taylor, and colleagues^{1, 2} com-

Abbreviations used

AQOL:	Asthma-specific quality of life
PEFR:	Peak expiratory flow rate
prn:	As needed
q.i.d.:	Four times daily

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pared four times daily (q.i.d.) use of inhaled dry powder fenoterol (1600 μ g/day) to as-needed (prn) use of β -agonists in a double-blind crossover study of subjects with mostly mild to moderate asthma. The regular use of this bronchodilator was associated with a deterioration of several measures of asthma control.

Albuterol use was examined recently in a review of data collected as part of a pretrial assessment of adults recruited for a study of the long-acting bronchodilator, formoterol. Three hundred forty-

one subjects with moderate asthma were randomized for 2 weeks of either regular or prn albuterol treatment, then crossed over to the other regimen.³ Metered-dose inhaler albuterol consumption was recorded in a diary on a daily basis. Only the last 8 days of each treatment period were analyzed. In contrast to the findings of Sears et al.,¹ peak expiratory flow rates (PEFRs) were not significantly different in the two regimens, and symptoms were actually less frequent with regular dosing.

In a more recent study of adults with mild to moderate asthma, twice daily administration of salmeterol was compared with q.i.d. administration of albuterol, 200 µg/day, and placebo in a 12-week randomized, double-blind, placebo-controlled, three-way crossover protocol.⁴ Although the primary intent of this investigation was to evaluate the effectiveness of salmeterol, a comparison of the regular versus prn albuterol groups did not reveal significant differences in symptoms, PEFR, or quality of life. In this study, too, albuterol use information was collected by subject self-reporting in a diary.

This study was designed to further examine the effect of regular bronchodilator use on asthma control. Individuals with moderate to severe asthma were studied, because the question of regular dosing is more relevant to this group. Two albuterol treatment regimens were compared: (1) two inhalations q.i.d. with prn supplements and (2) prn use only. Outcomes measured included prednisone requirements, morning and evening symptoms and PEFRs, total and nighttime prn albuterol use, pulmonary function test results, and asthma-specific quality of life (AQOL).

METHODS

Subjects

Adults with asthma were recruited from the outpatient allergy and pulmonary clinics at the University of Connecticut Health Center and St. Francis Hospital and Medical Center. All subjects had, within 1 year before study entry, a pretreatment FEV₁ of less than 80% of predicted value and 15% reversibility after bronchodilator administration.

Subjects had moderate to severe asthma, as defined by the National Heart, Lung, and Blood Institute Guidelines.⁵ Specifically, at least four of the following National Heart, Lung, and Blood Institute pretreatment criteria were required:

1. Exacerbations of cough/wheeze more than once or twice per week
2. Cough and wheeze between acute exacerbations often present

3. Reduced exercise tolerance
4. Nocturnal symptoms at least two or three times per week
5. School or work attendance compromised by asthma
6. PEFR less than 80% with a 20% to 30% variability
7. Periodic use of bronchodilators required during exacerbations for a week or more and systemic steroids usually necessary for treatment of exacerbations
8. Continuous, daily therapy often required to maintain control of asthma
9. Regular use of antiinflammatory medications required for prolonged periods

Participants were nonsmokers with less than a 10-pack-year history of tobacco use. Individuals with pulmonary diseases other than asthma or with significant cardiac disease were excluded. Clinical stability of asthma for 1 month before study entry was required. A subject was considered stable if medication doses had not been increased or prednisone added during that month.

Study design

The protocol was approved by the institutional review boards of the participating institutions; all subjects gave written informed consent before enrollment. This was a double-blind, placebo-controlled, crossover study with two 15-week treatment periods. At study entry, subjects were randomized to one of two albuterol dosing schedules: (1) QID+PRN, two inhalations q.i.d. with prn supplements or (2) PRN, two albuterol inhalations used prn for treatment of asthma symptoms. Subjects were evaluated in the clinic at 3-week intervals during the study. Regular asthma therapy was continued by the blinded investigating physicians throughout the study period. This included starting administration of prednisone or inhaled steroids or adjusting current doses according to the physician's assessment of disease severity from the history, physical examination, and spirometry. When prescribed, the prednisone dose was based on the physician's experience with that patient's previous exacerbations.

Throughout the study, subjects were instructed to use two inhalers: (1) the test inhaler, with contents blinded to the patient and investigators, to be used for two inhalations q.i.d. and (2) the rescue inhaler, which was open-label and contained albuterol, to be used prn for treatment of asthma symptoms. During the QID+PRN treatment period, the test inhaler contained albuterol; during the PRN period, it contained placebo. All albuterol inhalers delivered 90 µg per inhalation. Both test and rescue inhalers were housed in MDI Chronologs (MEDTRAC Technologies, Inc., Lakewood, Colo.), electronic devices that recorded the date and time of each actuation. MDI Chronolog output was used to determine test drug use and compliance and rescue albuterol requirement. Subjects were informed that the test inhaler contained either albuterol or placebo and that the Chronologs recorded the time and date of

inhaler actuations. Participants were explicitly instructed to use only the rescue inhaler for relief of symptoms. No other inhaled β -agonists were used by subjects. Other long-term medications were continued.

Outcome measures

The following variables were used as outcome measures during the study period: symptoms, PEFr, albuterol use, corticosteroid requirement, spirometry results, AQOL, and compliance with use of test drug.

Symptoms. Cough, shortness of breath, chest tightness, and wheezing were collectively recorded daily in diary format in the morning on arising and in the evening before retiring. A 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) was used for grading. The treatment period means for each subject were used for analysis.

PEFR. Three PEFrs were obtained daily in the morning and evening immediately after symptom recording, and the best PEFr was entered in the diary. Patients were instructed to measure PEFr before the use of any metered-dose inhalers. As with symptoms, the individual subject treatment period means for morning and evening PEFr were used for data analysis.

Albuterol use. Each patient's mean daily albuterol use for each treatment period was determined from MDI Chronolog output. Albuterol use was evaluated in three ways: (1) total daily rescue use, (2) nighttime rescue use, and (3) total daily albuterol consumption. Total daily rescue use was expressed as the number of rescue inhalations per day. Nighttime rescue use, or the number of rescue actuations per night, was determined with the times of awakening and retiring recorded daily in patients' diaries and the MDI Chronolog output. To eliminate actuations taken on retiring or awakening, only inhaler use for the period from 1 hour after retiring to 1 hour before arising was used for this variable. Total daily albuterol consumption included the sum of the daily rescue and test inhaler use. In the PRN treatment period, this was identical to the rescue use. This variable was expressed in micrograms of albuterol, assuming that 90 μ g was delivered per actuation.

Corticosteroid requirement. Corticosteroid requirement, especially prednisone requirement, served as a measure of the treating physician's assessment of disease severity and a marker of an exacerbation of asthma. Prednisone use was expressed as a percentage by using the following formula: (Number of days for which prednisone was required $\div$ Total number of treatment period days) $\times$ 100. Also, total milligrams of administered prednisone were compared for each treatment period. Finally, the day in each treatment period on which prednisone was first prescribed was determined. For inhaled steroids, the total mean daily dose for each patient in each treatment period was calculated in micrograms of corticosteroid with the rule that 1 actuation of beclomethasone delivers 42 μ g, triamcinolone 100 μ g, and flunisolide 250 μ g.

Spirometry. Prebronchodilator forced vital capacity, FEV₁, and forced expiratory flow, mid-expiratory phase at baseline and at the end of each treatment period were analyzed.

AQOL. AQOL was measured at baseline and at the end of each treatment period. The Asthma Quality of Life Questionnaire by Juniper et al.⁶ was used for this analysis. Each of the 32 items of this instrument is scored by using a 7-point scale, with 1 indicating maximum impairment and 7 indicating no impairment. The total score and domain scores of symptoms, activities, emotions, and environment were used as outcome variables. A change of 0.5 units or greater is considered clinically significant by the authors.⁷ This questionnaire has demonstrated responsiveness to pharmacologic intervention.⁴

Test drug compliance. Compliance with use of the test drug was determined for each day by the formula: (Total number of daily test inhalations $\div$ 8) $\times$ 100. Mean daily compliance for each treatment period was used for data analysis.

Statistical analysis

The individual subject means for each treatment period were determined for morning and evening symptoms, morning and evening PEFrs, total daily rescue albuterol use, nighttime rescue albuterol use, total daily albuterol consumption, and test drug compliance. Because of the relative lack of outliers among means over patients, a parametric test, the paired *t* test, was used for comparisons between treatment periods. Corticosteroid requirements were also compared with paired *t* tests. Baseline, post-QID+PRN, post-PRN spirometry, and AQOL values were compared by using analysis of variance for repeated measures. A *p* value of less than 0.05 was considered significant.

The daily data (PEFRs, symptom scores, albuterol use, compliance with the protocol) were examined for the presence of carryover effect by the following method, suggested in part by Fleiss.⁸ Group I was defined as those subjects receiving albuterol in the first treatment period and placebo in the second. Subjects in group II received placebo first. For group I, the mean effect (e.g., PEFr, symptom score, night rescue albuterol use) of the experiment for each subject could be expressed as $t_a + p_1$, where t_a is the effect of treatment (e.g., albuterol) and p_1 is the effect of being in the first temporal period. The effect of the experiment for group I in the second temporal period could be expressed as $t_b + p_2 + e_a$, where t_b is the effect of the other treatment (placebo), p_2 is the effect of being in the second time period, and e_a is the carryover effect of the first period (albuterol in this case). Similarly, the effect for group II in the first period is $t_b + p_1$; and in the second period, $t_a + p_2 + e_b$. S_I is defined as the average (period 1 result + period 2 result) for subjects in group I, for example, approximately $(t_a + t_b) + (p_1 + p_2) + e_a$. Similarly S_{II} is the average (period 1 result + period 2 result) for group II, for example,

TABLE I. Subject characteristics

Patient No.	Age at entry (yr)	Sex	Ethnic group	Age at DX (yr)	Baseline FEV ₁ (% predicted)	Night awakening/month*	Steroid days/year†
1	24	F	C	2	97	0	21
2	67	M	C	5	56	0	7
3	46	F	C	40	73	2	10
4	66	M	C	54	36	2	20
5	34	F	C	16	84	30	60
6	23	F	H	12	84	5	10
7	60	M	C	52	75	8	270
8	35	F	C	4	77	0	21
9	44	M	C	22	100	1	0
10	27	M	C	1	69	10	10
11	27	M	C	6	56	15	30
12	20	F	H	5	68	14	14
13	30	F	C	11	60	1	60
14	56	F	C	36	72	14	365
15	36	M	C	4	91	3	33
16	33	F	H	14	75	0	10
17	31	M	C	10	63	0	0
Mean	38 ± 4			16 ± 17	72 ± 16		55 ± 101

DX, Diagnosis; C, Caucasian; H, Hispanic.

*Night awakening in the month before entry.

†Number of days prednisone required in the year before entry.

approximately $(t_b + t_a) + (p_1 + p_2) + e_b$. Carryover effect is analyzed by comparing the "sums" of the results, S_I and S_{II} , by a two-sample t test of the means of each subject's sum.

Order effect was also analyzed; that is, patients who were first assigned PRN treatment followed by QID+PRN were compared with those assigned QID+PRN first. D_I and D_{II} were defined as the average differences for each subject in each group receiving albuterol then placebo; for example, for a subject in group I, $D_I \equiv (t_a - t_b) + (p_1 - p_2) - e_a$ and $D_{II} \equiv (t_a - t_b) + (p_2 - p_1) - e_b$. If there is no carryover effect (i.e., $e_a = e_b$), comparing the means of D_I for subjects in group I with D_{II} for group II subjects by two-sample t test describes the order or period effect.

A repeated-measures analysis of variance, breaking up the daily data in 3-week periods, was performed to examine time trends over each 15-week period.

RESULTS

Between March 1993 and September 1994, 23 subjects were enrolled. Six subjects were withdrawn from the study, leaving 17 who completed the protocol. Four of the six subjects were withdrawn because of noncompliance with the protocol (predominantly failure to make follow-up clinic visits). One subject withdrew from the study after a serious, unrelated illness developed, and one withdrew for personal reasons. The mean age of the dropouts at entry was 40 ± 10 years. Four were

Caucasian, one Hispanic, and one African American. At the time of withdrawal from the study, four were in the second chronologic treatment period. Three were following the QID+PRN regimen and three were following the PRN regimen at time of withdrawal.

The 17 subjects (8 men and 9 women) who completed the protocol are described in Table I. Baseline FEV₁ averaged $72\% \pm 16\%$ of predicted value (range, 36% to 100%). On entry, all but one were using inhaled corticosteroids, and two were taking prednisone regularly. None were taking theophylline or oral β -agonists. Nine had been hospitalized previously for asthma, seven more than once. One subject reported 20 such hospitalizations. Three had been admitted to an intensive care unit. Six subjects reported missing days of work because of asthma in the year before entry into this study. The range of missed days was from 1 to 7.

Thirteen subjects were atopic. The time of year of entry for subjects was well distributed among the seasons. There was a smoker in the home of only one subject.

Of the 17 subjects who completed the protocol, nine were randomized to the PRN schedule first and eight to the QID+PRN regimen. On average, there were 117 ± 18 days of follow-up for each

TABLE II. Symptom, PEFR, and treatment data

	QID + PRN	PRN	<i>p</i> Value
Corticosteroids			
Prednisone days (% of treatment period)	16 ± 26	24 ± 31	0.08
Mean daily dose of prednisone (mg)	2.72 ± 3.88	4.47 ± 5.79	0.03
Mean daily prescribed dose of inhaled steroids (μg)*	1530 ± 942	1449 ± 919	NS
Diary data			
Morning symptoms (0-3)	0.87 ± 0.59	0.87 ± 0.65	NS
Evening symptoms (0-3)	0.69 ± 0.56	0.72 ± 0.57	NS
Morning PEFR (L/min)	382 ± 120	359 ± 121	0.01
Evening PEFR (L/min)	415 ± 125	385 ± 120	0.001
Rescue albuterol use			
Total daily rescue albuterol (inhalations)	2.12 ± 2.24	3.29 ± 2.46	0.02
Nighttime rescue albuterol (inhalations)	0.21 ± 0.22	0.31 ± 0.29	NS

Values are expressed as means ± SD. NS, Not significant.

*Each actuation calculated as follows: beclomethasone = 42 μg, triamcinolone = 100 μg, flunisolide = 250 μg.

subject during the PRN period and 118 ± 20 days of follow-up during the QID+PRN period.

Compliance with the q.i.d. dosing of the test drug was $70\% \pm 25\%$ in the QID+PRN period versus $58\% \pm 27\%$ in the PRN period ($p = 0.056$). Two subjects set off their test inhalers more than 40 times successively on more than one occasion, usually preceding clinic visits, despite knowing the function of the Chronolog.⁹ These excessive uses were excluded from the statistical analysis. In addition, more than eight actuations of any canister within a 1-minute period were tallied as three actuations. In many cases this phenomenon was due to malfunctioning of the Chronolog device or depletion of the canister contents. This occurred approximately 10 times.

Total daily albuterol use (total rescue use plus test drug albuterol use in the QID+PRN period, total rescue use alone in the PRN group) was significantly greater in the QID+PRN group than in the PRN group: 702 ± 239 μg/day versus 296 ± 221 μg/day ($p < 0.0001$).

No subject required hospitalization or emergency care during either regimen. Table II compares the two schedules with respect to corticosteroid use, diary data, and daily rescue albuterol use. Prednisone requirements tended to be less in the QID+PRN regimen; that is, the percent of treatment days tended to be less during the QID+PRN regimen: $16\% \pm 26\%$ versus $24\% \pm 31\%$ of treatment days ($p = 0.08$). The average estimated amount of prednisone (in milligrams) required daily differed statistically: 2.72 ± 3.88 for QID+PRN versus 4.47 ± 5.79 ($p = 0.03$).

For five of 17 subjects, the first day of prednisone use occurred earlier in the QID+PRN

period; for five of 17, it occurred earlier in the PRN period; and for seven of 17, there was no difference. Thus there was no difference between treatment regimens in the time to the first requirement for use of prednisone.

Mean daily micrograms of inhaled steroid did not differ significantly between treatment periods (1530 ± 942 for QID+PRN vs 1449 ± 919 for PRN).

The two treatment periods did not differ significantly in morning or evening symptoms. Morning and evening PEFRs, however, were greater with QID+PRN compared with PRN scheduling: 382 ± 120 L/min versus 359 ± 121 L/min for morning PEFR ($p < 0.01$) and 415 ± 125 L/min versus 385 ± 120 L/min for evening PEFR ($p < 0.001$). Total rescue albuterol consumption was less in the QID+PRN group: 2.12 ± 2.24 inhalations per day versus 3.29 ± 2.46 inhalations per day ($p = 0.02$), although nighttime rescue use of this drug did not differ.

Table III outlines spirometry and AQOL data obtained at baseline and at the end of each treatment period. There was no significant difference in any of the spirometric values at the end of either period, nor was there any change from the baseline data. Although overall AQOL and some of its domains showed improvement compared with baseline for both treatment schedules, the two schedules did not significantly differ from each other. No carryover effect was found for any variable. There was no order effect for morning symptoms, morning or evening PEFR, 24-hour albuterol use, nighttime albuterol consumption, or total daily albuterol actuations. Order influenced compliance and evening symptom reports. Mean compliance was 70% for the first temporal period

TABLE III. Clinic visit data

	Baseline*	QID + PRN	PRN
Spirometry			
FVC (L)	3.8 ± 1.0	3.6 ± 1.1	3.8 ± 1.3
FEV ₁ (L)	2.5 ± 0.8	2.6 ± 1.0	2.4 ± 0.8
FEF _{25%-75%} (L/sec)	1.6 ± 0.8	1.7 ± 1.0	1.6 ± 0.9
PEFR (L/sec)	6.7 ± 2.0	7.2 ± 3.0	6.8 ± 3.0
Quality of Life			
Overall	4.29 ± 0.56	4.71 ± 0.67‡	4.69 ± 0.66†
Activities	4.39 ± 0.53	5.03 ± 0.63‡	5.05 ± 0.59‡
Symptoms	4.27 ± 0.54	4.54 ± 0.68	4.54 ± 0.67
Emotions	3.96 ± 0.77	4.31 ± 0.86	4.36 ± 0.89
Environment	4.19 ± 0.75	4.82 ± 0.76‡	4.57 ± 0.72

QID + PRN and PRN values represent end of respective treatment period measurements. Although quality of life significantly improved over baseline with both QID + PRN and PRN regimens, there was no significant difference between the treatment regimens in this outcome category.

FVC, Forced vital capacity; FEF_{25%-75%} forced expiratory flow, mid-expiratory phase.

*Baseline values were obtained at the initial clinic visit prior to randomization.

†Significantly different from baseline ($p < 0.05$).

‡Significantly different from baseline ($p < 0.01$).

and 58% for the second ($p = 0.07$, paired t test). The mean evening symptom score was 0.06 for first temporal period and 0.81 for the second ($p = 0.02$). The repeated-measures analysis of variance showed no time trends over the two temporal periods.

Subjects were not routinely asked whether they thought the test canister contained placebo or albuterol. Some thought we switched medications at each visit. Five of nine patients who were asked to guess whether they were receiving placebo or active drug responded correctly. One of these five, on another occasion, guessed incorrectly.

We did not use a hierarchy of outcomes as described by Sears et al.¹ Nevertheless, had their hierarchy been used, control would have been considered better for 13 during the QID+PRN regimen and for four during the PRN protocol ($p = 0.003$, Fisher's exact test). For 13 of 17 subjects, better control was determined by the number of days on which prednisone was required.

DISCUSSION

The purpose of this investigation was to compare the effect of regular versus intermittent dosing of albuterol in the treatment of moderate to severe asthma. Two 15-week albuterol treatment schedules were tested in a double-blind, crossover fashion: q.i.d. dosing with prn supplements

(QID+PRN) and prn use alone (PRN). Although patients were blinded to the nature of the test drug, the improved compliance when the canister contained albuterol rather than placebo (70% vs 58%) suggests that they consciously or unconsciously recognized its effect.

Despite more than double the daily consumption of inhaled albuterol during the QID+PRN scheduling, none of the asthma outcome variables significantly deteriorated during this period. Thus symptoms, nighttime rescue albuterol use, spirometry, and quality of life were not adversely affected by regular dosing. In fact, several outcome variables including total rescue albuterol use, morning and evening PEFR, and possibly prednisone requirement improved with q.i.d. dosing.

Use of electronic recording instruments rather than patient self-report of albuterol use should improve data collection on rescue albuterol requirements. The device also makes it possible to document nighttime use, a parameter that may be a very important marker of asthma severity.

The finding that total rescue albuterol use was less during q.i.d. dosing is not surprising because the regular inhalation of albuterol undoubtedly would have substituted for some of the prn daytime requirement for this drug. It should be noted that nighttime rescue bronchodilator requirement, which does not overlap with q.i.d. scheduling, was not different in the two periods.

Perhaps of more significance is the finding that morning and evening PEFR were significantly better during regular bronchodilator dosing. Because the evening PEFR measurement followed the last dosing of the q.i.d. schedule, improvement in this variable is understandable. The morning PEFR measurement, however, which was to be taken on arising before q.i.d. bronchodilator use, was 23 L/min higher during regular dosing.

Our findings differ considerably from those of Sears, Taylor, and colleagues^{1,2} who concluded that regular dosing of inhaled β -agonists led to a deterioration of asthma control. However, the two studies differ in several important areas. First, Sears et al.¹ tested the bronchodilator, fenoterol, a selective β -agonist not available in this country. It is uncertain whether these findings with fenoterol apply to other β -agonists. Interestingly, Chapman et al.,³ using albuterol, found results similar to ours, but the treatment periods were much shorter. Second, the sample studied by Sears et al.¹ had mostly mild to moderate asthma, whereas our sample had moderate to severe disease. It is unclear whether the detrimental effects

noted by Sears et al. apply to patients with asthma who have greater disease severity.

A third difference between this study and the study by Sears et al.¹ is the duration of the trials. In this study, subjects used regular albuterol for 15 weeks. Sears et al.¹ followed up their subjects for 24 weeks on each treatment arm but only analyzed the last 16 weeks of each of these periods. Because we observed no carryover effect, we analyzed all 15 weeks of each period. We suspect that this third difference between the trials does not contribute significantly to the differences in results between the studies.

Frequency of asthma exacerbations is another outcome measure noted to deteriorate with regular bronchodilator therapy in the study by Taylor et al.² In that group of patients, median time to first exacerbation was 33 days during regular fenoterol dosing compared with 66 days during prn bronchodilator use. Although we did not specifically evaluate for exacerbations, prednisone requirement was used as a marker of such exacerbations. Prednisone requirements tended to be higher in the PRN group, suggesting that exacerbations did not increase during the regular dosing period.

Even though each patient provided 30 weeks of data, our sample size is not large. Thus the possibility of a Type II error exists in outcomes in which no significant difference was observed. Nevertheless, even when significance was not attained, none of the trends suggest a detrimental effect from use of albuterol.

In conclusion, in our patients with moderate to severe asthma, q.i.d. albuterol dosing did not lead to deterioration of asthma control.

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