A Randomized Controlled Trial of Oral Albuterol in Acute Cough

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Background. Beta-agonist agents have been used for bronchospasm and cough in a variety of settings. We sought to evaluate the efficacy of oral albuterol for acute cough in ambulatory adults.

Methods. We performed a prospective, randomized, controlled, double-blind clinical trial comparing albuterol 4 mg by mouth three times daily for 7 days with placebo in 104 adults. Subjects had cough of less than 4 weeks' duration and no evidence of pneumonia, asthma, or chronic obstructive pulmonary disease. All subjects were enrolled at the walk-in clinic of a rural academic medical center.

Results. There was no significant difference between treated and control subjects in any measure of efficacy including cough severity score, reduction in sleepless nights, utilization of health care, or return to full activity. There were significantly more reports of "shakiness" and "nervousness" among albuterol-treated subjects than among controls.

Conclusions. Oral albuterol should not be used in unselected patients with acute, nonspecific cough.

Key words. Albuterol; cough; bronchitis; randomized controlled trials. (*J Fam Pract 1996; 42:49-53*)

Acute cough is common in ambulatory practice and a significant source of concern and of disability days. The vast majority of patients presenting with acute cough do not require treatment for a specific underlying condition, such as asthma, pneumonia, or chronic obstructive pulmonary disease (COPD). Currently, the only generally administered treatments for adults are oral cough suppressants and antibiotics. Most coughing patients have no evidence of bacterial infection and thus do not benefit from antibiotic therapy.

Beta-agonist drugs are widely used in cough due to asthma and COPD. Asthma with cough as the sole symptom is well described and appears to respond well to beta-agonist therapy.[1] Beta-agonists increase the cough threshold to irritants in normal subjects[2] and stimulate mucociliary clearance.[3] A study of terbutaline in chronic "allergic" cough indicated that there was a significant improvement in daytime and nighttime coughing.[4] Salbutamol, the British name for albuterol, has been shown to be effective for nighttime coughing[5] but was reported to have little effect on severity or frequency of cough during the day. In this study, all the patients were thought to have "acute respiratory infection," but no mention was made of specific antibiotic treatment.

A prior randomized trial compared albuterol elixir with erythromycin for adults with acute bronchitis.[6] Albuterol-treated patients were less likely to be coughing after 1 week and had no more side effects than did the antibiotic-treated group. This study did not include placebo controls. Two other studies compared inhaled albuterol to placebo in adults with bronchitis and found a significant reduction in coughing at 7 days[7] and an improvement in spirometry with a nonsignificant improvement in symptoms.[8]

We sought to confirm the results of prior studies[5,6] of the effects of oral beta-adrenergic agents on patients' symptoms in outpatient therapy of acute cough. We chose oral albuterol rather than an inhaled beta-agonist because it is less expensive and does not require extensive patient instruction to ensure that patients receive an effective dose.

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Methods

We performed a randomized, double-blind, placebo-controlled trial of albuterol in ambulatory adults with acute cough. The trial was performed in the adult walk-in clinic at Dartmouth-Hitchcock Medical Center between October 1992 and May 1994. The study protocol and patient consent procedures were approved by the institutional review board.

Eligible patients included all adults with nonspecific bronchitis or acute cough of less than 4 weeks' duration. We excluded patients if they were pregnant; were at risk for cardiac arrhythmia by virtue of known cardiac disease or history of arrhythmia; used any form of systemic or inhaled corticosteroids during the week prior to presentation; had findings of lung consolidation or infiltrate on physical examination or radiograph; had been treated for asthma or COPD within the past 10 years; used any form of beta-agonist medication by any route during the week prior to presentation; used any tricyclic antidepressant or monoamine oxidase inhibitor; had a contraindication to beta-agonist therapy, eg, arrhythmia, allergy, recent myocardial infarction; or refused consent.

All eligible patients were evaluated by the faculty or house staff physician on duty in the clinic. Diagnostic studies, including radiographs, spirograms and analysis of blood, were performed at the discretion of the clinician. If the physician judged that antibiotics were indicated, erythromycin 333 mg by mouth three times daily for 7 days was prescribed. If other antibiotics or corticosteroids were indicated, the patient was excluded. Physicians prescribed dextromethorphan cough suppressants or codeine at their discretion.

Patients were stratified by antibiotic use and then randomly assigned to either albuterol or placebo. Each patient was issued a vial of identical-looking pills prepared by the study pharmacist. The vials were labeled with the instructions "Take one pill three times a day for seven days." The active pills contained albuterol sulfate 4 mg. The control pills contained only a calcium carbonate filler. Randomization was achieved by a computer-generated random number assigned to each vial of medicine in the pharmacy. Large boxes of vials were delivered to the clinic and thoroughly mixed. Separate boxes were maintained for patients on antibiotics and those not taking antibiotics. The clinic staff chose one vial from the proper box for each patient and recorded the vial number.

At study entry, the nurse and physician completed a data record on each patient recording identification data, vial number, demographics, and symptoms. Clinic staff instructed each patient to complete a daily diary of symptoms for 1 week after the visit and instructed patients on how to take the study medicine and to return the diary. A research assistant contacted each patient during the week as a reminder to complete the diary and again 1 week later if the diary had not been promptly returned.

For each day of the study, the patient diary included data on severity of the cough as measured by a previously tested 4-point scale[9] (0=none, 1=mild, 2=moderate, and 3=severe); use of cough-suppressants; interruption of sleep by cough; visit to any health care provider for cough; participation in work, school, or other usual activities as measured on a 3-point scale (0=none, 1=partial activity, and 2=full activity); use of the study medication; and presence of side effects, including nervousness, dizziness, shakiness, and headache. The main outcome variable was the average cough severity score as measured by a 4-point scale (range 0 to 3) over days 2 to 7.

The main a priori hypothesis was that albuterol would affect the mean severity score compared with that of placebo. We also hypothesized that other outcomes, such as sleeping through the night, returning to activity, headache, and nervousness, would be different between the two groups. Further, we considered that some combination of patient characteristics and treatment variables may produce a valuable descriptive model of outcomes. We undertook exploratory analyses to find such models without specific a priori hypotheses. We used chi-square tests to compare categorical variables. Continuous variables generally were not normally distributed and were compared with Wilcoxon rank sum tests. We employed linear regression to simultaneously study the effect of several variables.

Results

Characteristics of the Study Population

One hundred forty-two patients enrolled in the trial and 104 completed their diaries, for a completion rate of 73%. Respondents and nonrespondents were similar with regard to sex, duration of cough at entry, severity scale at entry, randomization to albuterol, and prescription of dextromethorphan or codeine (Table 1). Nonrespondents were significantly younger ($P<.001$). The remainder of these analyses were done on subjects with analyzable diaries.

Among the 104 respondents, 45% were men, the mean age was 43 years with a median of 40.5 and a range of 19 to 74. The mean duration of cough was 9.5 days with a median of 7 and a range of 1 to 28 days. The study population is further described in Table 1. We asked a subsample of 32 subjects to guess whether they had received active or control tablets. Eighty-four percent cor-

Table 1. Patient Characteristics at Enrollment

	Treated Subjects	Control Subjects	*P* Value
Subjects lost to follow-up, n	20	18	
Mean age, y	30.1	33.7	.60
Sex, % male	35.0	38.9	.84
Duration of cough, d	8.8	12.2	.33
Mean severity score, 0–3 scale*	2.25	2.22	.90
Subjects who returned full diaries, n	51	53	
Mean age, y	42.6	42.6	.78
Sex, % male	43.1	47.2	.68
Duration of cough, d	9.3	9.8	.49
Mean severity score, 0–3 scale*	2.12	2.15	.88
Current smoker, %	14.3	28.3	.28
Productive cough, %	50.0	52.8	.85
Cough awakens patient from sleep, %	76.9	77.4	.99
Fever by history, %	57.1	34.0	.11
Temperature >38.0° C on exam, %	7.1	1.9	.38
Wheezing on forced exhalation, %	35.7	18.9	.18
Prolonged expiratory phase, %	14.3	24.5	.41
Antibiotics prescribed, %	60.8	73.6	.16
Dextromethorphan prescribed, %	56.9	52.0	.62
Codeine prescribed, %	43.1	28.0	.11

**Higher score indicates greater severity.*
NOTE: Values in some cells are based on fewer subjects because of missing data.

rectly identified their treatment status. This proportion was similar in both treatment groups.

Primary Analysis: Effects of Albuterol

We found no significant difference between albuterol-treated and control subjects in any measure of efficacy, including severity score, sleeplessness, utilization of health care, or return to full activity (Table 2). Cough severity scores improved over time in both groups, but the rate of improvement did not differ with treatment. A similar proportion of patients were still coughing at 7 days in both groups (placebo 73% vs albuterol 78%, $P=.53$) (Figure). There were significantly more reports of shakiness and nervousness among albuterol-treated subjects than among controls. There was little difference in reported dizziness or headaches.

Table 2. Results Among Subjects Receiving Oral Albuterol and Those Receiving Placebo

Variable	Treated Subjects* (n=51) Mean (SD)	Control Subjects* (n=53) Mean (SD)	*P* Value†
Severity, 0–3 scale‡	1.46 (0.63)	1.52 (0.56)	.44
Activity, 0–2 scale§	1.04 (0.64)	1.01 (0.68)	.74
Days using additional medications	3.8 (2.8)	3.2 (2.7)	.29
Sleepless nights	2.6 (2.3)	3.0 (2.2)	.26
Additional health visits	0.08 (0.27)	0.09 (0.30)	.77
Days of nervousness	1.00 (1.68)	0.26 (0.73)	.04
Days of dizziness	0.37 (0.87)	0.41 (0.86)	.70
Days of shakiness	2.02 (1.97)	0.34 (0.71)	<.001
Headache days	1.35 (1.63)	1.25 (1.73)	.57

**54.9% and 66.0% of treated and control subjects, respectively, reported full compliance with study medication, P=.25.*
†P values are calculated using Wilcoxon rank sum tests for continuous data and chi-square tests for rates.
‡Higher score indicates greater severity.
§Higher score indicates greater activity.
NOTE: Outcome measures were calculated over 6 days excluding the day of initial visit.
SD denotes standard deviation.

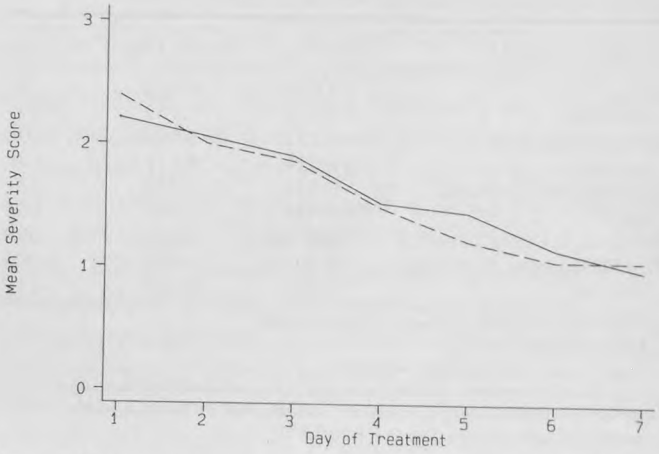

Figure. Mean severity score over time by treatment group. The vertical axis represents the subjective severity score on a scale of 0 (no cough), 1 (mild), 2 (moderate), 3 (severe). The horizontal axis shows the duration of treatment. The lines represent the mean score at each day for control patients, represented by the solid line, and albuterol-treated patients, represented by the broken line. Although both groups improved over 7 days, they did not differ significantly at any time.

Secondary Analyses

Effects of Cough Suppressants

Dextromethorphan may have had an effect on some symptoms. The mean activity score was significantly better in the dextromethorphan group (1.3 vs 0.8, $P=.001$). The sleep score, ie, the number of nights with sleep interrupted by cough in the 6 days after treatment was begun, was significantly lower in patients who used dextromethorphan (3.2 nights vs 2.3 nights, $P=.04$) as was the number of days with headache (1.0 vs 1.6, $P=.03$). The mean cough severity score was marginally lower in the dextromethorphan group (1.3 vs 1.6, $P=.07$). Dextromethorphan was not randomly allocated in this study; physicians prescribed it without specific guidance from the study protocol. Therefore, there is reason to believe that the dextromethorphan-treated group may have been different from the rest of the subjects in clinically observable ways.

To compare our results with that of previous work,[5] we examined the effect of albuterol among the subgroup of patients given dextromethorphan. The mean severity

Table 3. Regression Analysis of Mean Severity Score

Predictor Variable	Coefficient	Standard Error	*P* Value
Albuterol	+0.059	0.182	.75
Antibiotic	+0.111	0.162	.49
Cough suppressant	+0.232	0.133	.09
Codeine	−0.024	0.114	.83
Albuterol and antibiotic*	−0.334	0.219	.13
Age, y	+0.010	0.003	.004
Sex†	−0.274	0.102	.009
Baseline severity, 0–3 scale‡	+0.307	0.085	<.001
Constant	+0.304	0.243	.21

**1=both albuterol and antibiotic; 0=one or neither.*
†1=male; 0=female.
‡Higher score indicates greater severity.
NOTE: Numbers represent ordinary least-squares regression with mean severity score as dependent variable. Positive coefficients indicate that the presence of the variable worsened outcome. Overall, $P<.001$, $R^2=0.379$.

score was identical in the albuterol (1.60) and control (1.60) groups ($P=.99$). We found a nonsignificant improvement of 0.8 sleepless nights with albuterol in this subgroup (2.8 vs 3.6, $P=.22$). This effect falls to 0.3 when controlling for baseline sleeplessness ($P=.52$ for albuterol vs placebo).

Effects of Antibiotic Use

Patients who received antibiotics had results similar to those of patients who did not. The mean severity score was 1.5 in both groups ($P=.70$). Among the 34 patients who received no antibiotics, there was a trend toward worsening with treatment (1.3 in the control group vs 1.6 in the albuterol group, $P=.16$). However, among subjects who took erythromycin, there was a trend toward improvement with albuterol (1.6 in the control group vs 1.3 in the albuterol group, $P=.08$).

Treatment Interactions

We investigated the apparent interaction between albuterol and erythromycin with linear regression analysis using mean severity score as the dependent variable. The independent variables were age, sex, and severity score on day 1 (before treatment) and binary variables representing treatment with albuterol, erythromycin, or cough suppressants (either dextromethorphan or codeine) and an interaction term for simultaneous treatment with both albuterol and erythromycin. Age, sex, and baseline severity were significant predictors, but none of the treatment variables were significant at $P<.10$ except use of cough suppressants. About one third of the variability in severity was explained by the model (Table 3). We interpret this analysis to suggest a modest clinical effect of cough suppressants but no significant effect of any of the other treatments when controlling for baseline characteristics.

Discussion

Although earlier research has reported evidence that oral albuterol is useful for adults, our data suggest otherwise for nonspecific cough. An early report[5] studied dextromethorphan alone and in combination with salbutamol (albuterol) 2 mg three times per day for 4 days. The investigator found that the combination therapy was more effective than dextromethorphan alone in suppressing nocturnal cough, but no differences were found in daytime symptoms. We used a higher dose of the drug for a longer period and did not require all albuterol-treated subjects to take dextromethorphan. However, we found no additional benefit of albuterol, even among our subjects who received dextromethorphan.

A more recent study[6] compared albuterol 2 mg four times per day with erythromycin. Among the 17 patients in each group, fewer albuterol patients were coughing at 7 days (41% with albuterol vs 82% with erythromycin, $P=.004$). We found that 78% of albuterol patients were coughing after a week's treatment compared with 73% of placebo patients ($P=.53$). Why did we find no effect when other authors did? Our study included three times as many patients and used a higher dosage. We also studied placebo controls rather than those taking antibiotics. It is possible that the single outcome measure of coughing at 7 days is more prone to random error than is the week-long severity index that we used. It is also possible that if we had used a different dose or the inhalation form of albuterol, we may have shown similar results. We have no data to support this conjecture.

The latest study from the same group[7] compared inhaled albuterol with placebo. Patients were also randomized to receive either erythromycin or placebo, but the full results of this comparison were not reported. That study enrolled 23 patients in each group and reported improvements in cough at 7 days and in return to work but not in other symptoms. Nine patients were cough-free at 7 days in the albuterol group compared with two in the control group ($P=.02$). These results may be explained by a greater benefit and fewer side effects associated with inhaled vs oral albuterol. The small sample size and the concentration on a single point in time for the outcome measure may have magnified the possibility of a false-positive result.

A study from Norway[8] used inhaled fenoterol or placebo in 73 patients. It reported a 5.1% improvement in FEV_1 with treatment and 0.5% with placebo. This small difference reached statistical significance ($P=.006$). There was a small improvement in symptoms in the treated group as compared with the control group, which did not reach significance. These authors demonstrated a high prevalence of hyperreactive airways, as determined by

methacholine challenge or other abnormal lung findings, in their study group and present data to suggest that essentially all of the apparent benefit occurred in this subgroup. This study differs from our report in enrolling a large number of subjects with hyperreactive airways and using inhaled fenoterol rather than oral albuterol.

During post hoc analysis, we found weak evidence for an interaction between albuterol and erythromycin. The relationship was of borderline statistical significance and minor clinical import. We do not consider it a proven association. Similar complaints should be lodged against our findings that dextromethorphan appears useful in this setting. Neither erythromycin nor dextromethorphan was randomly assigned in our study. Physicians may have prescribed them for different types of patients. Therefore, the apparent effects of either of these medications or their interactions with albuterol could be the result of baseline differences in subjects rather than in inherent effectiveness.

This trial measured the effectiveness of albuterol in a generalizable clinical setting rather than efficacy in a tightly controlled laboratory environment. We sought to understand if albuterol worked when used by physicians in the heterogeneous manner in which they tend to prescribe it. Therefore, we did not control many of the simultaneous treatments. Nor did we perform extensive diagnostic evaluation to isolate a homogeneous population of patients with specific diagnoses, such as post-viral bronchospasm or acute tracheobronchitis. This design adds variability to the results but improves generalizability. Our results should apply to many similar clinical settings and are not restricted to a narrow range of subjects with a narrow range of co-treatments. We restricted antibiotic choice to erythromycin because it is a reasonable therapy for most bacterial upper respiratory tract infections and because the choice of another drug may indicate a broader differential than we anticipated. Restricting the trial to patients not receiving any antibiotics would have produced essentially the same results.

Although our study was formally double-blinded, we have evidence that unblinding was common. The side effects of albuterol were so pronounced and the impact of the placebo so small that nearly all patients correctly guessed their treatment status. In spite of this loss of blinding, the dropout rates were similar in both treatment groups, and subjects did not report an improved outcome even when they knew they were taking the active drug. Loss of blinding should bias a trial in favor of the active treatment, but we did not observe such a bias.

For a negative trial, such as this one, it is important to ensure adequate power to detect a clinically important difference.[10] Using mean severity score as the main outcome measure, we observed a statistically nonsignificant difference of 0.06 points between groups with a standard deviation of 0.60 points. With 50 subjects in each group and requiring a P value less than .05, we had a better-than-80% chance of detecting a difference as small as 0.35 points, if it was present. A sufficiently large study of approximately 3140 subjects would assign statistical significance to the difference we observed. We feel such a small difference would have little clinical import.

This randomized, double-blind, placebo-controlled trial of oral albuterol in adults with acute nonspecific cough showed no evidence for efficacy but did demonstrate significant toxicity. Oral albuterol should not be used in this setting.

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